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ALTERATIONS IN THE VOLUME OF THE NORMAL SPLEEN AND THEIR SIGNIFICANCE. BEING THE 21ST MARY SCOTT NEWBOLD LECTURE OF THE COLLEGE OF PHYSICIANS OF PHILADELPHIA. By JOSEPH BARCROFT 1

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THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JANUARY, 1930

ORIGINAL ARTICLES.

ALTERATIONS IN THE VOLUME OF THE NORMAL SPLEEN AND THEIR SIGNIFICANCE.

BEING THE TWENTY-FIRST MARY SCOTT NEWBOLD LECTURE OF THE COLLEGE OF PHYSICIANS OF PHILADELPHIA.

BY JOSEPH BARCROFT,

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THE work of three men whose names appear on the roll of this College, Pearce, Krumbhaar and Frazier,[1] has to me been so great a source of inspiration as to make this evening one which will always stand out in my memory. The pleasure, of discussing the change of volume of the spleen in Philadelphia is as great as the sense of honor which I feel in being asked to do so by a society which numbers among its members some of those whose opinions on this subject are of outstanding authority. My own methods are perhaps different from most used by them and my only regret is that the occasion is that of a lecture rather than a medical exchange of experience.

Let me commence by stating very shortly, and so disposing of, certain inevitable methods of technique.

The object has been to form some estimate of the alterations in volume of this spleen when the animal is in full health and exercising his normal functions. Anesthetics must be barred and even the plethysmographic methods, so fruitful in the hands of Hargis and Mann,[2] and of Heymans,[3] have not been used because they postu-

late quiescence on the part of the animal. I have had recourse to two principal methods of investigation:

1. That of performing a preliminary operation in which small metal clips were placed along the edge of the spleen, and when the effects of the operation had entirely worn off, judging of the size of the organ by means of Roentgen ray photographs taken in the horizontal and vertical planes; from which photographs a presentable reconstruction can be made of the lineal outline (Barcroft[4] and others).

2. An operation by which the spleen, without injury to its vascular and nervous attachments can be withdrawn through the body wall and fixed in a position outside of the skin. In this position the organ rapidly makes itself at home, so much so that it ultimately becomes covered by a delicate epithelium like that of the lip and is then proof against any but gross injury (Barcroft and Stevens[5]).

By either of these methods large alterations in the volume of the organ may be seen rapidly to take place. So large indeed are they as to convince the observer that the spleen may on occasion contain perhaps one-fifth of the whole blood volume.

The principal experimental procedures which will lead to the rapid disgorgement of this blood are, asphyxia, carbon monoxid poisoning, exercise, hemorrhage, and as has been shown by Hargis and Mann,[2] and by Cannon and Izquierdo,[6] emotion.

I pass over these acute effects very briefly because they have already been described in print and I pass to certain effects which extend over longer periods of time, concerning which less has been already published. One comment, however, I must first make in the cases of hemorrhage and of exercise: the contraction of the spleen, is not as I had once supposed, a final effort on the part of the body to add to the blood volume. It is a very early effect, a kind of fine adjustment; like all fine adjustments, though useful, is not indispensable.

Prolonged Contraction of the Spleen. *The Effect of Pregnancy.*[7] The first experiments in which the spleen was exteriorized were, of course, somewhat of a speculation. These were carried out in the early summer of 1926. When the phenomenon of the contraction of the spleen on exercise had been fully established it became our intention to take one, at least, of the three animals in our possession to show at the Physiological Congress at Stockholm. The question was which should it be? We placed the dogs in an order of merit and the order remained undisturbed until a few days before the date of departure for the Congress. Then the spleen of our best animal suddenly became small and pale. The animal itself became extremely disinclined to take exercise and when it did so the contraction of the already small spleen was not very well marked. We were, of course, greatly disappointed, partly because our best specimen had failed and partly because the possibility was introduced that the exercise contraction of the spleen was a less constant phe-

nomenon than we had supposed. However, two quite good specimens remained. These were taken to Stockholm where the best alas was run over in the street by a motor bus. The remaining animal, however, proved quite a convincing demonstration of exercise contraction.

To return to the animal which we decided not to take. It was killed just before we started; our laboratory assistant Sergt.-Major Secker, R. A. M. C., performed a postmortem upon it and on our return from Stockholm we were greeted with the information that the uterus of the animal had contained fetuses in a fairly advanced stage of development. It must be confessed that we did not at once grasp the significance of what had taken place.

A second "accident," however, focussed our attention on the subject. We exteriorized the spleens of two dogs. Both spleens ran a somewhat similar course for a while, then one suddenly became much smaller and pale. It had shrunk in a few days to half its surface. Then one morning we came into the laboratory to find 7 puppies. From this time the spleen gradually enlarged. Ultimately partly because of the continued gradual shrinking of the spleen of the control animal and partly because of the gradual enlargement of the spleen of the recently pregnant one, the two became almost the same size.

From this time we undertook some systematic observations in the subject of the relation of pregnancy to spleen volume.

The technique at first was similar to that which has just been described. A bitch was "covered" by a dog: at the same time another of about the same size was chosen as a control. Four to five weeks afterward the spleens of the two were exteriorized. As the period of gestation in the bitch is sixty-three days, there remained about four weeks and a half in which the spleen could settle down. Usually it is not possible to make any comparisons which are of value for the first ten days. The size of the spleen depends upon the operative procedure for that period—a little more or less pressure on one of the splenic vessels will make a considerable difference. After that, about ten days, the comparisons between the "probably" pregnant and the control bitches were instituted. In each case there was little to choose in size between the spleens of the two animals at that stage, but in the last fortnight or ten days' pregnancy, the spleen of the prospective mother shrank to an insignificant size and became very pale, enlarging again after the birth of the pups and ultimately attaining the size of that of the control animal. Once the spleen had attained the same size they ran a pretty equal course, both gradually shrinking for a time. The least satisfactory feature of these experiments was that we were comparing the variations in the size of the spleen of the pregnant bitch not with a control whose size remained the constant or practically constant, but with one which itself was gradually shrinking. At that time we had not

discovered that after the spleen has been exteriorized for several months the volume changes relatively little. That discovery was made on an animal which had been used as a control in one of the above experiments. After her spleen had settled to a volume of relative constance it happened that she came on "heat." She took the dog successfully and so we had the opportunity of investigating the effect of pregnancy on a bitch whose spleen, apart from the demands of her reproductive organs would have remained of relatively constant volume over a period of nine weeks.

The spleen showed a marked but passing contraction during the period of "heat." This was only a matter of a few days. It returned to its former size and no material alteration took place until nearly half way through the pregnancy. The spleen then commenced to shrink and reached its minimum size about four days before the birth of the pups. During those four days it altered but little, growing if anything, but directly after the pups were born the spleen rapidly became more turgid and within twenty days it was larger than at any time during the previous six months. Such is a rough outline of the facts. There are one or two points to be cleared up before we discuss their interpretation.

There is usually a certain amount of anemia associated with the exteriorization of the spleen. Could it be that the alleged pregnancy shrinkage was really a result of anemia, not in truth a primary result of pregnancy. Hemoglobin determinations were made throughout the course of the experiment last quoted. The hemoglobin percentages were as follows:

Three months before pregnancy	Hb = 80.0
During heat	Hb = 74.6
During first half of pregnancy	Hb = 75.6
During second half of pregnancy	Hb = 70.2
During twenty days after	Hb = 72.2

The above results show that during the period of "heat" when the spleen was contracted, the hemoglobin values were not sensibly lower than they had been previously. Throughout the whole of the pregnancy they remained in the vicinity of 70 with one or two exceptions, at which level they were at the time of birth and for some time subsequently. Moreover the research of Shen[8] showed that, while bleeding caused a shrinking of the spleen, the fact of a low hemoglobin value did not necessarily do so.

Postoperative Contraction of the Spleen. During the course of experiments in which parts of the intestine were exteriorized,[9] some time after exteriorization of the spleen, some quite unexpected observations were made.

In the first two experiments of the series a loop of small intestine was withdrawn and placed outside the abdominal wall.[10] In both cases the animal seemed to do well even though the gut had not been severed and the food had to pass along the exteriorized portion.

Neither dog, however, lived very long, the ultimate trouble in each case being perforation. In one animal the lesion was in the abdominal cavity. The dog suddenly became ill; the condition clearly being hopeless, it was killed. The postmortem examination showed a general infection of the abdomen.

The perforation in the other animal took place in the exteriorized portion; it was due to an accidental cause, namely, that the dog swallowed a piece of bone about 4 inches long. This was unable to get round an angle where the gut was fixed to the abdominal wall. In both these cases the spleen became quite small during the operation and did not regain the size thereafter. Indeed in the first case, that in which general peritonitis developed, the spleen shrunk even more than it had done; it was at its smallest when the animal died.

The question arose: Had these animals survived, would their spleens ever have attained to a size as great as that which they would have occupied if the subsequent abdominal operation had never been performed?

One experiment has taken place in which a portion of gut has been exteriorized with perfect success by Florey,[11] after the spleen had been exteriorized some two months previously. There was no indication of any general or even local infection. Nevertheless, the spleen again shrank to about half the previous size and remained so for about four weeks. After that time it dilated and attained the size which judging from a control dog, it would have occupied if no intestinal operation had taken place. Here again we are in the dark as to whether the contraction was due to a nervous reflex or to some substance absorbed from the wound or elsewhere.

Significance of the Splenic Contraction. Having studied some of the phenomena, for their own sake, which the contraction of the spleen presents, we may now turn to the consideration of the question of what significance may be the splenic contraction. Let us go back to Gray's original thesis that the function of the spleen is to control the quantity and quality of the blood.

The Regulation of the Quantity of Blood. Three factors appear to be connected, though the precise numerical relation between them is not as yet worked out.

1. The volume of blood in the body.

2. The volume of the bed in which it circulates, that is, the pressure under which the blood would be in the body if the whole circulation ceased.

3. The volume of blood which circulates per minute round this vascular system over short periods of time.

If, for instance, a certain quantity of blood is injected into the circulation, all observers (Daly,[12] H. Barcroft[13] and Jarisch[14]) agree that, other things being equal, the circulation rate will be increased.

They agree moreover that in the closed heart-lung preparation

or in the intact but brainless animal the rate of increase expressed in cubic centimeters per minute is of the order of ten times the amount of blood injected. Thus, as will be seen from the following picture, roughly 20 cc. of blood injected will produce an increased flow of 200 cc. of blood per minute round the body.

Suppose then a dog to have a bloodflow of 1 liter of blood per minute round his body and suppose that the spleen adds to that 100 cc. of blood. The increased bloodflow is found by multiplying the 100 cc. of added flow by ten, and is therefore 1 liter. The effect then has been to increase the ratio of bloodflow from 1 to 2 liters per minute.

In the case of exercise such an increase forms an appreciable proportion of the whole augmentation which takes place.

Moreover, the significance of the addition of blood from an outside source, such as the spleen, does not end with the statement which has just been made.

Among the various factors which conspire to give momentum to the blood when exercise is taken, is the augmentation of the depth of respiration.[15] Now if I understand aright, the effect of deepened respiration on bloodflow is not so much to add to the velocity of the circulating blood, but to multiply it by a factor.

Let me ask a question. If a certain degree of dyspnea increased the minute volume of blood from an initial value of 1 liter to a final value of 2 liters, would the same degree of dyspnea augment an initial value of 2 liters into a final value of 4 liters? I am not prepared to make definite statement in the affirmative, nevertheless there does seem to be that element about the effect of dyspnea. It is a sort of amplifier and therefore any other factor which adds to the minute volume, has in exercise a significance beyond the face value owing to this effect of the dyspnea which follows and amplifies it.

The word "follows" if not actually used advisedly is used not quite casually. The events which lead up to exercise are often gradual and, as the result of suitable emotion contraction of the spleen, may precede the actual exercise, in which case the splenic increase of the minute volume would precede so much of the dyspnea as is caused by altered hydrogen-ion concentration of the blood.

Hemorrhage. Let us pass to the significance of hemorrhage in relation to spleen volume.

Striking as are the results produced by the injection of blood, the results produced by its withdrawal are perhaps more so. The withdrawal of 100 cc. of blood from a closed heart-lung preparation reduces the minute volume of blood from 1.5 liters per minute to 0.5 liter per minute. But so far as is known, a very early effect of hemorrhage on this intact animal is to produce contraction of the spleen

and in the cat about $\frac{1}{15}$ of all the blood may be taken from the vessels without any sensible fall in the volume of the circulating blood. Applied to a dog of 15 kilos, that would mean that 100 cc. of blood could be taken out without appreciably reducing the quantity of blood in circulation. After that 100 cc. had gone, the minute volume would commence to pay a heavy tax on every further cubic centimeter of blood withdrawn.

More Chronic Compensations. Apart from the rôle of the spleen in buffering mechanically the vascular system against sudden emergencies in the circulation such as those caused by hemorrhage, exercise, etc., there remained to be considered such questions as the rôle in pregnancy, intestinal operations, alterations in skin temperature, etc.

About these matters we know but little; a calculation made on the basis of some work by Uyeno[16] suggested that the total volume of blood which coursed through the skin vessels if dilated by heat might be about 3 liters in man per minute. This is of course associated with a considerable increase in the size of the vascular bed in the skin vessels. Clearly these alterations could be effected without any alteration in the total minute volume, of the total vascular capacity by the cutting off of blood from other areas. But to supply 3 liters of blood per minute to the skin would on that basis mean the diversion of anything from 40 to 90 per cent of this whole bloodflow to the skin and have little for the essential organs of the body. It seems rational therefore that if the vascular bed is enlarged the blood volume should be enlarged in proportion, that is to say, so that the blood exerted the normal pressure in the vessels. And indeed experiments, other than the original observations on our way to Peru,[17] have shown an increased bloodflow as the result of residence in a warm chamber. The provision of corpuscles to meet the increased bloodflow may be a legitimate function of the spleen; the matter could easily be tested on an animal with an extracutaneous spleen, but that has not been done.

Operations. We are still more in the dark as regards the shrinkage of the spleen in intestinal operations. Here the weak point in the argument is not whether or no the spleen contracts, but whether or no there is any commensurate increase to the vascular bed. This matter again is under investigation.

Pregnancy and Heat. The evidence with regard to these alterations is on the whole more satisfactory than with regard to either postoperative shock or exposure to warm climates, because we know that we have both a large increase in the vascular bed of the generative organs and a decrease in the size of the spleen. The point unproven here is the actual increase in the blood volume in dogs. But insofar as it is legitimate to transfer information culled from one form of life to another, these experiments seem to form a natural

complement to those of Rowntree,[18] who found a rise with vital red in the blood volume much beyond the amount of the fetus—the method was that of vital red injection which in any case could not by the very nature escape from the maternal blood. The rise commenced about the middle of pregnancy, the same time as did our contraction of the spleen.

Regulation of the Quality of the Blood. As Regards the Blood Count. Many observers now have studied the effect of contraction of the spleen upon the blood count—a problem which has been attacked in more than one way. The most direct attack was that of Cruickshank,[19] who in the cat cut the splenic nerves and by tying nearly all of the anastomatic vessels reduced the lienal circulation to almost a simple system in which the blood entered the organ by the splenic arteries only and left it by the splenic vein only. He could then rapidly clamp the splenic artery, stimulate the splenic nerve and, collecting the blood which was evacuated from the spleen, determine its hemoglobin content. To give an example in which stimulation yielded 8 cc. of blood from the cat's spleen, the following were the hemoglobin values of each cubic centimeter, that of the arterial blood being taken as 100:

Cubic centimeter:—1st	2d	3d	4th	5th	6th	7th	8th
Hemoglobin value . 100	104	120	135	126	..	108	96

These results show at a maximum an increase of 35 per cent in the red corpuscles and on the average about 15 per cent. The addition of 8 cc. of such blood to that of the whole animal would not appreciably alter the erythrocyte count of the blood in the general circulation.

The above results fall far short of what might be expected from the experiments of numerous investigators who have produced indirect evidence of the effect of the splenic contraction on the red blood count. Their procedure has been to institute some experimental condition, asphyxia, adrenalin injections, exercise, etc., observe the consequent rise in the blood count and compare the results with that produced on a control splenectomized animal.

The most complete of such experiments are perhaps those of Scheunert and Krzywanek[20] who showed that the red count in the horse may rise from 6.01 million to 8.04 million on work. This means a 33 per cent increase in the red blood corpuscles. I cannot see how that could be effected solely by the spleen, even if the spleen contribution was 100 per cent corpuscles. Moreover, everything that we know about the mechanism of the body suggests that too large an alteration is only likely to be affected as the result of a combination of causes working in unison. Every adaptation is an integration.

Binet and his school have carried out a great many experiments

of this type of which the following by Binet and Williamson[21] is a fair example:

	Red blood cell in millions per c.mm.
Dog-chloralose:	
Normal before asphyxial crisis	7.4
Normal after five minutes asphyxia	8.6
Normal before second asphyxia	7.7
Normal after five minutes asphyxia	8.4
Dog-chloralose:	
Normal before first asphyxial crisis	8.0
Normal after five minutes asphyxia	9.8
Splenectomized before second asphyxial crisis	8.8
Normal after five minutes asphyxia	8.8

In a form of life so widely different from the mammals as the dogfish, Hall and Gray[22] have observed what appears to be essentially the same phenomenon. Reduce the oxygen content of the water in which the fish is contained, the spleen contracts and the red blood corpuscle count rises.

The question naturally arises, can such result be obtained on man? Himwich and Barr[23] in 1923 showed that exercise in man raised the oxygen capacity of the blood; these observations have been confirmed by the subsequent work of Harrison, Robinson and Syllaba.[24] Pickering and Syllaba[25] have, however, tried the same experiment on a number of splenectomized persons, in whom they also obtain an increase in oxygen capacity. If there is any difference then between the normal and splenectomized individuals it is at most a small differential one.

Iron. One of the striking appearances exhibited, especially by unstained sections of the spleen, is that of a brown material known as hemosiderin. A good deal of controversy has taken place about this substance, first as to whether it is always in cells or is sometimes free, and second, as to whether it is a compound more or less on the hematin level, as opposed to a compound of iron of a more simple nature. As regards the first point, I can offer no opinion. I have certainly seen it outside actual cells, but whether or not the cells which may have contained it broke down in the processes to which the sections were treated, I am unable to say.

As regards the nature of the pigment, it must be admitted that, as usually found, it does not give the usual tests for inorganic iron such as those with potassium sulphocyanate, potassium ferrocyanide or potassium ferricyanate. It does, however, give a black coloration with ammonium sulphate. The recent work of Stanley Cook[26] seems to indicate that in spite of these facts, hemosiderin is nothing more complicated than ferric hydrate, but in some sort of colored suspension. Hemosiderin is seen not only in the spleen pulp, but often in large quantities in the sinuses which go to form the confluents of splenic vein and in the splenic vein chiefly it follows that when the spleen contracts such hemosiderin (that is, $Fe_2(OH)_6$) as may be in the venous sinuses and the vein itself is driven on.

What becomes of it is as yet unknown. Nor is it known whether the number and strength of the splenic contractions have any influence on the rate of the production and, therefore, over any long time of its elimination.

The Fragility of the Red Corpuscles. Orahovats,[27] using essentially the same preparation as Cruickshank had done, studied the relative fragilities of the red blood corpuscles which enter and leave the spleen and obtained positive results. To graduated salt solutions, the corpuscles in the blood squeezed out of the spleen are more fragile than those of the general circulation. The interpretation of this observation is not very easy. One or both of two reasons might be ascribed. First, residence in the spleen might increase the fragility, or second, the spleen might filter off the more fragile corpuscles. As between these two views, the evidence which he adduced seemed to favor that which seemed inherently least likely, namely, that the spleen exercised some kind of selection, and the facts would be explained if we assume that in proportion to its fragility the corpuscle has a greater chance of sticking in the spleen.

Though these experiments were suggested to us by those of Pearce, Krumbhaar and Frazier, who showed that the fragility of the corpuscles varied for some time after the spleen had been cut out, and though our results are what might be expected, they will, I think, agree with me that the ultimate interpretation of both is not at all certain.

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THE AGRANULOCYTIC BLOOD PICTURE IN CONDITIONS OTHER THAN ANGINA.

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Since 1922, when Schultz called attention to the condition, an increasing number of cases of so-called agranulocytic angina has been reported, both in Europe and in this country. The picture painted by Schultz was characterized by the occurrence, usually in elderly females, of a necrotizing throat infection, with fever, rapidly developing exhaustion, slight jaundice and a quickly fatal issue with the blood picture of leukopenia, an almost complete absence of granulocytes, and almost complete lack of involvement of the red cells and platelets.

Since Schultz's article appeared, it has become apparent that all cases do not conform strictly to his original description. In some, contrary to his specifications, hemorrhagic symptoms have been present and in others involvement of the red cells with pronounced anemia has occurred. It has become clear that the necrotizing process does not necessarily involve the throat but that the gums, the esophagus, the intestines, the genitalia and even the skin may be attacked.

It is the purpose of this paper to point out that local and general sepsis not affecting primarily the skin or mucous membranes may be accompanied by a leukopenia and an agranulocytic blood picture and to discuss the differentiation of these conditions from others which may simulate them.

While four cases have been observed, only one came to autopsy. A brief description of this case, observed on the service of Dr. Francis G. Blake in the New Haven Hospital, will serve as a point of departure.

Case Report. C. M., a Scandinavian loom mechanic, aged fifty-two years, entered the medical service of the New Haven Hospital June 25, 1928, having been referred there for the treatment of glycosuria.

His chief complaint on entrance was lung trouble and weakness.

He stated that for three weeks before entrance he had been unusually fatigued, and that during this period he had lost 15 pounds in weight. He had also had a series of boils on his forearms. Two weeks before entrance he developed a cold, with chilly sensations, cough, slight dyspnea and purulent morning expectoration. There was anorexia and nausea, but no vomiting. He was constipated.

The past history was quite eventless. He had had the usual minor ailments of childhood but had never been sick since. There was no venereal or alcoholic history. There had been no serious injuries or operations.

His family history was without significance. His parents died at an advanced age and he had five healthy children.

On entrance to the hospital he had a temperature of 100° F., a pulse of 88 and a respiration of 20 to the minute. He was poorly nourished and his skin was sallow, subicteric. The teeth showed caries and there was an area of reddened, swollen and slightly tender gum where a tooth had been removed several weeks previously. The chest was noted to be emphysematous but the examination of the other organs showed nothing of note.

The *urine* had a specific gravity of 1012, showed the slightest possible trace of albumin, no sugar and was otherwise normal.

The blood, June 25, showed red blood corpuscles 3,100,000, hemoglobin, 60 per cent, leukocytes, 2600. The differential count, stated in the history to be probably incorrect, showed polymorphonuclears, 61 per cent; lymphocytes, 39 per cent, large mononuclears, eosinophils and basophils none. The appearance of the red cells was said to be normal.

June 27. The leukocyte count was 1600, with a differential count of polymorphonuclears, 54 per cent and lymphocytes, 46 per cent.

June 28. The leukocytes were 1800.

On June 29 swelling of the left thigh with fluctuation was noted. The patient left the hospital against advice on this date.

July 14 the patient returned to the hospital with swelling and tenderness of the left thigh. He had been in bed since his return home and had developed during that time a second tooth abscess which ruptured spontaneously.

He was transferred to the surgical department of the hospital where a large abscess of the thigh was opened and drained. Cultures from this showed Staphylococcus aureus. He was noted at this time to be subicteric with negative heart and lungs, a liver palpable at the costal margin and no enlargement of the spleen. There were a few palpable posterior cervical lymph nodes.

A blood count July 15 showed: red cells, 2,500,000; hemoglobin, 75 per cent; leukocytes, 4250. The differential count showed polymorphonuclears, 2 per cent; lymphocytes, 36 per cent; large mononuclears, 62 per cent. The Wassermann reaction was negative.

Three blood cultures were taken which all showed different organisms. The first, Staphylococcus albus, the second a Gram-negative bacillus, the third Bacillus pyocyaneus. These were probably all contaminations. He ran a moderate fever, and never showed any splenic or glandular enlargement. There was no marked change up to the time of the patient's death, July 29, 1928.

Further blood counts: July 16. Red blood cells, 2,200,000; hemoglobin, 75 per cent; leukocytes, 3000.

July 24. Red blood cells, 2,600,000; hemoglobin, 75 per cent; leukocytes, 2000. Differential polymorphonuclears, 5 per cent; atypical mononuclears, 95 per cent.

Autopsy was made by Dr. George Wilson two hours after death. Anatomical diagnosis:

Primary. Hyperplasia of the bone marrow, generalized lymph node enlargement, splenomegaly, acute gingivitis, multiple petechial hemorrhages into the submucous and subserous surfaces, focal necrotizing pneumonia.

Subsidiary. Ulcerative periostitis of the left femur, hydrocele of the right testis, fibrous thickening of Glisson's capsule.

The microscopic examination did not show the usual lesions of lymphatic leukemia. There were no accumulations of lymphoid cells in any of the viscera. The bone marrow was hyperplastic. Megakaryocytes were scattered through the tissue and normoblasts were present, but the tissue was predominantly made up of agranular leukocytes and embryonic white blood cells.

In summary, then, a man, aged fifty-two years, with a negative family and past history developed an illness characterized by the occurrence of root abscesses in two teeth, exhaustibility, cough and expectoration, anorexia, fever, loss of weight and an ulcerative periostitis of the thigh. Physical examination showed no clinical enlargement of the spleen or lymph nodes, a palpable liver, and a blood picture of moderate anemia with marked leukopenia and almost complete absence of granulocytes. Death was apparently due to sepsis, exhaustion and a terminal focal pneumonia. The postmortem examination showed a hyperplastic bone marrow but did not show the usual histologic picture of lymphatic leukemia.

An examination of the literature shows that somewhat similar cases have been reported from time to time for over twenty years.

In 1904, Schwartz[1] reported the case of a boy, aged nine years, with a renal or perinephritic abscess which ruptured into the urinary tract. There was improvement for a time but after several weeks the boy developed gingivitis, swelling of the submaxillary glands and a leukocyte count of 600, the differential count showing no polymorphonuclear cells. Only a brief abstract of his paper is available and the report is not entirely satisfactory.

Türk,[2] in 1907, reported a case of staphylococcus sepsis with peculiar changes in the blood and bone marrow. The patient, a previously well woman, aged forty-five years, developed general malaise, pains in the right flank and cough. Later fever with chills, headache, anorexia and still later diarrhea occurred. There was high fever, stupor, an embolic skin eruption, a mitral murmur, a patch of consolidation in one lung, and a few slightly enlarged lymph nodes. There was some ulceration of the lips and in places necrosis of the gums. Before death, which occurred about a month after the onset of the illness, the spleen was palpable, the sternum and ribs were tender and the tonsils were covered with an opaque white membrane. The blood on entrance showed 5,245,000 red cells, 92 per cent of hemoglobin and 940 leukocytes. Of the leukocytes 93.5 per cent were lymphocytes, 4.4 per cent large lymphocytes, 0.6 atypical mononuclears, and 1.5 per cent basophils. The platelets were slightly increased. There were slight changes in size and shape of the red cells. A subsequent differential count showed 96.1 per cent lymphocytes, 2.23 per cent large mononuclears, and 0.55 per cent basophils. Cultures from the skin lesions showed Staphylococcus aureus. A blood culture was negative.

The autopsy showed sepsis with fresh endocarditis, lung abscess, and no evidence of leukemia either in the gross or in sections. Staphylococcus aureus was recovered from the blood. The bone marrow appeared normal except for small hemorrhagic areas. Microscopically, most of the white cells in the marrow were lymphocytes and plasma cells.

In 1912, Stursberg[3] published a paper on the differential diagnosis

between acute leukemia and sepsis. He cited the case of a husky blacksmith, aged forty-one years, who, in 1910, was operated on for osteomyelitis of the arm. In the fall of 1911, he developed bleeding from the nose and mouth, increasing pain in the mouth and dysphagia. Examination showed swelling of the cheeks with a brownish-red discoloration of the mucosa and swelling of the tissues of the face and neck. There was fever. The spleen was not felt and the internal organs showed no demonstrable change. There were numerous petechiæ and suggillations on the legs. The patient died the day after admission. The leukocyte count was 900 and no granular cells were seen in counting 408 leukocytes. There were 399 lymphocytes, 8 large mononuclears and 1 lymphoblast. The red cells showed no change in morphology.

The autopsy by Ribbert showed nothing of moment. The spleen was not enlarged. The long bones showed fatty marrow. There was no sign of leukemia either in the gross or microscopically. The erythroblastic part of the marrow was unaffected.

In 1913, F. Marchand[4] reported the case of a man, aged twenty years, with weakness, increasing pallor and bleeding from the gums. There were small bloodclots on the lips and blood on the posterior pharyngeal wall. The lymph nodes in the neck, axillæ and groins were slightly enlarged. The heart was slightly enlarged and showed a soft systolic murmur. The liver was slightly and the spleen markedly enlarged. There was blood in the stools and retinal hemorrhages. The urine contained albumin and urobilin.

The blood showed 1,500,000 red cells; hemoglobin, 35 per cent and 2100 leukocytes. The differential count showed polymorphonuclears, 6.5 per cent; transitionals, 8 per cent and lymphocytes, 85.5 per cent. Death occurred after an illness of about a month with a clinical diagnosis of acute lymphatic leukemia.

The autopsy showed no signs of leukemia. The long bones contained fatty marrow. The organs showed hemorrhages. There were small, nonsuppurative embolic lesions in the lungs and brain. Those in the lungs contained streptococci. It was a case of pyococcal sepsis with agranulocytosis.

In a paper on lymphocytosis published in 1928, Kenneth McAlpin[5] records the case of a child, aged three years, with a history of fever of five months' duration. He had slight swelling of the face, swollen lymph nodes and a marked anemia. Some of the nodes in the neck were incised and Staphylococcus aureus was obtained. The internal organs showed no demonstrable clinical change. The leukocytes on admission were 2100 with 32 per cent polymorphonuclears, 65 per cent lymphocytes, and 3 per cent mononuclears. His final count showed 1200 leukocytes of which 8 per cent were polymorphonuclears, 68 per cent lymphocytes, 12 per cent mononuclears and 12 per cent smudges. A blood culture shows Staphylococcus aureus and the postmortem showed innumerable abscesses in the viscera.

It is evident that in this group of patients, as in those with agranulocytic angina, we are dealing with individuals whose bone marrow reacts differently to bacterial infection than does that of most patients. It can hardly be argued that this peculiarity in reaction is an inborn permanent condition, for in agranulocytic angina, where a much larger number of cases is available for study, there are instances where the same patient has reacted with the usual polymorphonuclear increase to one attack of an infection and has shown an agranulocytic reaction to another attack. It is a moot question, on which there is a good deal of disagreement, whether the bone marrow condition precedes the local infection or follows it. If it is assumed to precede it, and certainly in some cases the patient is ill before the development of local lesions, we are only pushed a step farther back for we must then account for the condition of the bone marrow. Something, perhaps some toxin, damages the bone marrow in such cases and paralyzes its ability to form granulocytes. It is natural to think of this action as a toxic one from analogy to the known effects of chemical substances such as benzol, thorium and other agents on the bone marrow. There is evidence in some cases, on the other hand, that in the early stages of the infection there is still granulocyte formation and that the agranulocytosis becomes more and more pronounced as the infection progresses. This suggests the infection as the cause of the bone-marrow lesion. There is, of course, evidence in the cases that recover that the damage to the bone marrow is not permanent and irreparable. In the present state of our knowledge this question must be left open.

From the point of view of diagnosis, sepsis with agranulocytosis raises great difficulties, chiefly because certain blood diseases such as leukemia and aplastic anemia, in which there is also agranulocytosis, are frequently accompanied by terminal infections, especially about the mouth and throat.

So far as acute leukemia is concerned I feel that we must agree with Stursberg and Marchand that a diagnosis during life between the so-called aleukemic type of lymphatic leukemia and sepsis with agranulocytosis is not possible. I am aware that some observers claim to be able to make a differentiation on the morphology of the blood but I doubt this. A final decision can only be reached in the pathologic department.

With aplastic anemia, the difficulty of diagnosis is not so great, at least in typical cases. In agranulocytic sepsis, the power of the marrow to form red cells is often but little damaged, so that the very low red blood counts usually observed in aplastic anemia are not found. The leukopenia and agranulocytosis are common to both diseases. Nevertheless recent experience has led to the conclusion that there are patients with an aplastic type of anemia of obscure origin, that is, not obviously secondary to a known toxemia, who may have a fairly high red blood count and there are patients

with an agranulocytic infection who may have quite a low red blood count. The subject is one which demands further critical study.

Conclusions. 1. There are cases of local and general sepsis with an agranulocytic blood picture, aside from the well-recognized group of agranulocytic anginas.

2. It is not yet clear whether the sepsis or the loss of power of the bone marrow to form granulocytes is the primary lesion.

3. Such cases cannot be differentiated clinically from acute aleukemic lymphatic leukemia with terminal infectious processes.

4. In some instances it may be difficult to differentiate them from aplastic anemia with terminal infection.

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ANGINA PECTORIS; IS IT ALWAYS DUE TO CORONARY ARTERY DISEASE?*

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Angina pectoris is a clinical syndrome with no definitely recognized pathology and as such its limits are difficult to state and so there may be doubt as to whether a given case should be so designated. However, there are certain features which are usually regarded as characteristic in a general way: (1) There is severe pain which is referred to some part of the sternum or beneath it. (2) There are certain common causal features, exertion, emotion or anger, a heavy meal (especially with any of the other factors) and exposure to cold. (3) There is an immediate enforced cessation of activity. (4) The pain tends to radiate. (5) Sweating is common. (6) The attack is relieved by rest, nitrites and morphia. (7) The patient is usually in his normal state within a few days at most.

Recently there is an increasing tendency noted in articles to consider that these symptoms are due to coronary artery disease exclusively and the possibility of any other cause is regarded as out of consideration. With this in some cases has been the inclusion of the features of acute coronary artery occlusion as a special form of angina pectoris. This seems to be unfortunate, as it tends to put under one heading a condition with definite clinical features and a

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positive lesion with a group which is much less definite. In one condition there is a syndrome (angina pectoris) with uncertainty as to the cause in some cases, without a definite pathology and with an uncertain outlook. In the other (acute coronary artery occlusion) there is a very definite etiology and pathology with a prognosis which can be reasonably estimated. The treatment of the two conditions differs in many respects. Is it wise to group them together?

I speak of frank coronary artery occlusion and not of coronary artery disease in general, or of what may be termed slight chronic occlusion. My feeling is that there are a number of causes of angina pectoris, of which cardiac disease is one but not the only one. If we regard these symptoms as always due to coronary artery disease, with which I am specially concerned, or its effects, how are we to explain the following groups of cases? I quite realize that one case may prove nothing but it can raise doubts.

1. *Angina Pectoris and Coronary Artery Occlusion in One Patient.* A man, aged sixty years, who led a high-pressure life, for two years had attacks of angina pectoris. He had moderate arteriosclerosis, no evidence of renal disease, had not had syphilis, and usually had a blood pressure of 150 to 160 systolic and 90 diastolic. He was given to fits of anger on slight provocation. On the day on which I first saw him, when coming to my office his motor was struck by another car and while no great damage was done he became very angry, so that a severe attack of angina pectoris began and was well developed on his arrival. He showed the usual picture with a gray look, severe suffering and profuse sweating. The pulse and blood pressure showed no change. He was relieved rapidly by nitroglycerin and morphia. His pain was referred to the upper sternum and radiated into the neck and down the left arm. He outlined the situation of the pain very definitely and was emphatic that it was never over the lower sternum or precordium. Afterward he said that he expected death in each attack. He went on reasonably well if he took care for about two years. Then came a different attack in the form of an acute coronary artery occlusion. He was not far from the hospital where he was brought at once and I saw him a few minutes later. The picture was definite, with severe pain referred to the lower sternum and both sides of it, marked collapse, a rapid feeble pulse, a blood pressure of 90 systolic, with the diastolic difficult to determine. Later he had fever and a pericardial friction rub. After this he was an invalid and died about six months later. He did not have another attack of what I regarded as angina pectoris. Of course, he was quiet and there was no overexertion but there were fits of anger.

Here is the point of particular interest. After he had recovered somewhat from his attack of acute coronary artery occlusion, he volunteered the statement that this attack was different from any

he had before, with a different situation and a different pain. When asked how the pains differed he said "I cannot describe these pains but they are not the same. You cannot describe the difference between the taste of a strawberry and a pineapple."

In another patient there was much the same story. I did not see him in any of the angina pectoris attacks but his physician had seen him in several and the description left little doubt of their nature. I saw him in an attack of coronary artery occlusion. He also was very emphatic in his statement that the pains were different in character and situation. In his earlier attacks the pain was felt below the upper sternum; in the coronary occlusion attack beneath the lower part of the sternum.

Another example of pain of different situation was seen in a young adult who had syphilitic aortitis and also syphilitic myocarditis. I am aware of the difficulty of being certain of the latter, but this diagnosis was apparently justified. The patient volunteered a description of two kinds of pain, one felt under the upper sternum, the other under the lower sternum and to the left. The pain which we regarded as due to the aortic disease, referred to the upper sternum, was the more severe and brought on by very slight exertion. It occasionally came on without any evident causal factor. She did not have attacks which we regarded as angina pectoris.

A few patients regarded as having angina pectoris have described two varieties of pain, one referred to the upper sternum and the other referred to the lower sternum and precordium. One patient, who had marked dilatation of the aorta and whose symptoms dated back for three years, stated that it was the pain felt over the upper sternum which radiated down the left arm; the lower sternal pain never did. My suggestion is that the upper sternal pains in these patients were due to aortic disease.

2. *Duration of Symptoms.* If all the features of angina pectoris are due to coronary artery disease what happens in the patients who have severe attacks for many years? If each attack of angina pectoris is due to something occurring in the coronary distribution, perhaps in a very small branch, there hardly seems enough vascular territory to supply sufficient material. An example is as follows: A physician had his first severe attack of angina pectoris in 1896 and was seen by Sir William Osler, who told me that he did not expect him to recover. He went away for a long rest and afterward resumed his work. He recognized his limitations and did very well but emergencies were very apt to bring on an attack. Exertion beyond a certain point always did so and he knew very accurately how much was safe. He had often spoken to me of his symptoms but first consulted me in 1910. His attacks were the most severe that I have ever seen. The pain was first felt in the back and "came through," as he expressed it, to the front. He could not localize the pain exactly; it was felt over the greater part of the

sternum and to the left. There was intense suffering. He threw himself on his back, stretched his arms out at right angles to his body and very quickly took the position of opisthotonos, resting on his head and heels. Morphia gave prompt relief. Nitroglycerin had done so before but had lost its effect. As a rule the pulse rate remained at 72; the highest in any attack which I saw was 84 for a very short time. The heart showed no particular change and the blood pressure hardly altered from a systolic figure of 140 and a diastolic of 90. He died in an attack.

Over a period of fourteen years this patient had many attacks, not all of maximum severity, although the majority were severe. He died without any evidence of serious cardiac change. Could all these attacks have been due to coronary artery disease? They may have been due to spasm but, if this was marked, why was there not more change in the action of the heart?

3. *The Group Associated with Esophageal or Gastric Symptoms.* This group is one which has puzzled us all, I am sure. An example is under observation at present. The patient, aged sixty-seven years, is well preserved, with moderate arteriosclerosis and a heart which shows no particular evidence of disease. His attacks have occurred for a period of four years and as a rule begin with a feeling of gastric distention and a desire to belch, soon followed by pain. Years ago he had done gastric lavage himself for indigestion and it occurred to him that if he passed a stomach tube at the first sign of any distress he might obtain relief. His idea was correct but some one told him that it was dangerous and it was regarding this that he consulted me. I advised him to continue with it and for three years he has been able to prevent every attack becoming severe with one exception. This began when he was unable to get his stomach tube promptly and was severe, requiring morphia and nitroglycerin. He is careful with regard to diet and overexertion, but the effect of the passage of the stomach tube in cutting short an attack seems well established.

How are we to regard such a case? If due to reflex spasm of the coronary arteries, one might suppose that the relief of gastric distention could be responsible, but it does not seem likely that a patient, aged sixty-seven years, has coronary arteries which are capable of much spasm. If there is some change, such as occlusion of a very small branch, how can his procedure influence this? The reverse may occur. In one of my patients the first attack of angina pectoris came on while a biliary drainage was being done. There are some cases apparently secondary to gall-bladder disease in which after removal of gall stones the attacks of angina cease. What is the mechanism here? You may suggest coronary spasm but it is about as easy to deny as to assert its probability. I recently saw a remarkable case with my associate, Dr. Martin Rehfuss, whom the patient consulted for difficulty in swallowing.

He was given barium and while Dr. Rehfuss was examining him before the screen there was a sudden esophageal spasm with spasmodic contractions. The patient made severe efforts to belch without success and then suddenly a very severe attack of thoracic pain began.

4. *Angina Pectoris Apparently Secondary to Disease Elsewhere.* A man, aged forty-seven years, came with a history of two years of attacks of thoracic pain which were growing more frequent and more severe. He had seen a number of consultants who agreed on the diagnosis of angina pectoris. He had read extensively about it, had made up his mind that "Death was just round the corner waiting for me" as he put it and expected each attack to be his last. Examination showed no evidence of any disease of the circulation but there was evidence of a severe prostatitis and inflammation of the verumontanum with marked tenderness. Treatment of this was begun at once with rapid improvement in his general condition and a gradual disappearance of the attacks of thoracic pain. That is twelve years ago and he has remained free of the symptoms of angina pectoris ever since.

How is one to explain such a case as this? Clinically, there seemed no question of the character and severity of the attacks. His physician had seen him in a number of them and stated that he had expected him to die in several of the attacks. His wife gave a very graphic description of them. Were they due to coronary spasm or to spasm of the aorta? Was there some definite change in a coronary artery with each of them? The last is difficult to believe. This case suggests that a purely nervous mechanism may be at work. In recent literature this possibility receives scanty attention but it appears to be the most reasonable explanation for some cases. The studies of Libman on the individual variations in response to pain must be remembered in this connection. There is also the group in which the first manifestations of an attack are in the periphery, for example in the arm. Later there is substernal pain.

5. *The Influence of Myocardial Insufficiency on Angina Pectoris.* The usual rule is that when symptoms of myocardial insufficiency appear, the attacks of angina pectoris stop. This is not invariable, as in one patient who was seen in several attacks of angina pectoris, which did not begin until after the onset of decompensation. His pain was always felt beneath the upper sternum. If the myocardium struggling to work with an insufficient blood supply and anoxemia are essential and invariable factors in the causation of angina pectoris, why should this be? The patients who have had angina pectoris and then a frank coronary artery occlusion do not seem to have any more attacks of the former after the latter has occurred.

6. *The Occurrence of Angina Pectoris in Patients with Dilatation of the Aorta.* As a rule the attacks of pain in these patients do not

have the usual characteristic features of angina pectoris but some of them do. The pain is referred to the upper sternum and may radiate down both arms or down the right arm only.

These points may be regarded as of small importance when taken singly, but considered together it seems to me that they present a strong argument against the syndrome termed angina pectoris being always due to coronary artery disease or necessarily to heart disease of any kind. You may say that the question has been asked but not answered, and I agree, but these points seem arguments against an exclusive coronary artery etiology.

The use of the term angina pectoris, with our present knowledge, cannot be governed by set rules, but the majority of us would agree that it is a combination of clinical features which are fairly definite. The pain may be felt beneath any part of the sternum, but I should insist on the importance of the relationship to the sternum. Pain felt about the apex of the heart only is probably not due to angina pectoris. Angina pectoris may appear later in such a case.

There are possibilities of many variations and differences in the several features. We would agree that while we may sometimes be in doubt from a patient's description of his attacks, there is rarely any question if we witness an attack. Is it not a mistake to include under this syndrome with its uncertainties such a definite picture as is presented by acute coronary artery occlusion? Why put a clear-cut entity into an indefinite group when it has been separated after many years of confusion? We all agree that many cases previously regarded as angina pectoris are due to coronary artery occlusion.

As to the factors which cause angina pectoris, it seems most reasonable to regard it as having a multiple etiology. Disease of the aorta in some cases, of the coronary arteries and myocardium in others, probably of both in some cases, seems definitely established. That other causes may operate seems probable in the way of viscero-sensory reflexes. May these represent spasm largely? It may be entirely possible but the possibility of a nervous mechanism alone should not be entirely neglected.

Summary. 1. Angina pectoris is a clinical syndrome with fairly marked features but without any definite single causal pathologic change. It should be clearly distinguished from *acute* coronary artery occlusion which has a definite pathologic basis.

2. The statement, frequently made, that angina pectoris is always due to coronary artery disease does not seem to be supported by the evidence. The same may be said of the view that it is always due to a "tired heart muscle."

3. There are probably several factors which may be operative in causing an attack, in the aorta, in the coronary arteries and myocardium and in the nervous system. It is doubtful if disease of any one structure can explain all cases.

THE INVOLVEMENT OF THE CORONARY ARTERIES IN RHEUMATIC FEVER.

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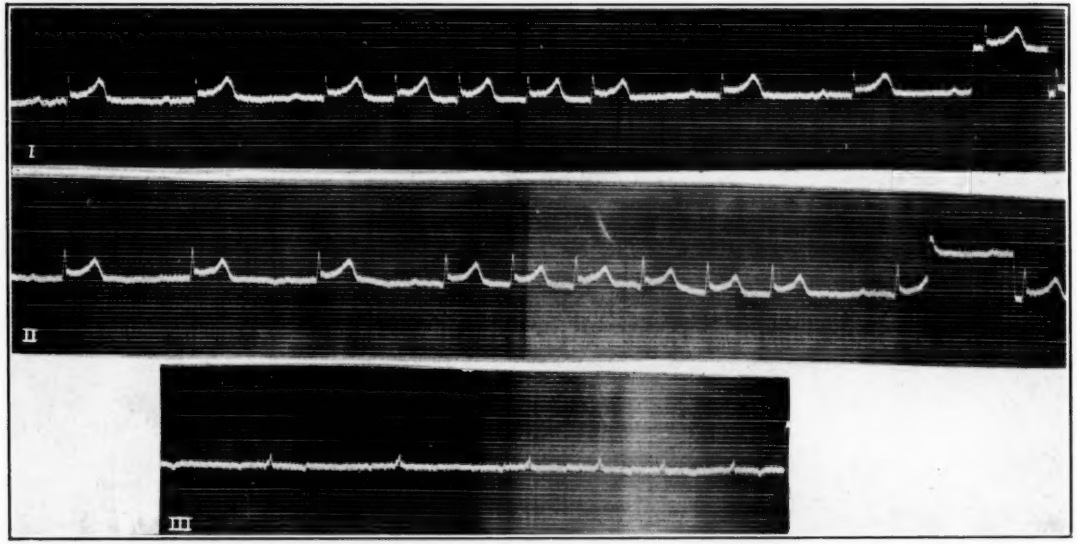
Our interest in the specific changes in the vascular system in rheumatic fever particularly as affecting the coronary vessels was stimulated by the case to be cited. This case occurred in the wards of the Jewish Hospital of Brooklyn, N. Y., on the service of Dr. Alex L. Louria. It is with pleasure that I acknowledge my thanks to him for the privilege of reporting this case and his many kindly suggestions.

Case Report. M. G., female, aged thirty-six years, married, was admitted on January 10, 1928. Her previous history was unimportant except to note that she had been admitted three times previously for surgical conditions at which times no subjective or objective cardiovascular symptoms were demonstrated. In June, 1927, six months prior to admission, she began to complain of slight dyspnea, precordial distress, epistaxes, weakness, pallor and a progressive loss of weight (20 pounds). On January 7, 1928, she was suddenly seized with extremely severe pain in the epigastrium radiating to the right anterior chest and right arm, relieved only by large doses of morphin. On admission, she was dyspneic and vomited, and on examination was in shock and in great pain; there was an anxious expression on her face, her forehead was covered with cold perspiration, her throat was congested. Her pulse was irregular and slow, 48 per minute, the heart sounds were of poor quality and the heart was moderately enlarged. A diagnosis of coronary closure with partial heart block was made. The next day an enlarged tender liver was noted, a localized friction rub appeared to the left of the sternum, and concomitantly a leukocytosis and a moderate temperature developed. From then on to January 21, 1928, she ran an irregular temperature, with frequent nosebleeds, fugacious pain and swelling of the various joints. These subsided promptly on the administration of salicylates. She felt well until January 25, 1928, when again her temperature rose, nosebleeds recurred and her joints were again successively involved. The response to salicylates was again prompt. On the last day of January, 1928, her temperature was normal. A soft systolic murmur had appeared at the apex, the heart was widened. She felt well until February 21, 1928, when she again developed repeated epistaxes, an acute follicular tonsillitis, following which her joints again became swollen and tender. Her temperature again rose, varying between 101° F. and 103° F. This lasted two weeks, the symptoms being relieved by salicylates. Blood cultures, chemistry of the blood and Wassermann reactions were negative. The electrocardiogram at the time of her admission showed the *T* waves coming off midway on the down limbs of *R* in Leads I and II (see illustration). Later electrocardiograms showed the gradual inversion of the *T* waves which in later tracings became upright.



The large *T* waves of Leads I and II come off almost midway on the down limb of the *R* waves. The *T* of Lead I is frequently higher than the *R* and almost as high as the *R* of Lead II.

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Discussion. The history for six months before her last admission was such as to suggest to us invasion of the myocardium by the rheumatic virus. Suddenly, three days prior to her admission, she developed a coronary occlusion. The electrocardiogram showed the findings we recognize as occurring in closure of a large branch of the coronary artery.[1, 2, 3, 4, 5] That no such electrocardiographic finding as that illustrated occurs in uncomplicated rheumatic fever has also been demonstrated (Parkinson, Gosse and Gunson,[6] Cohn and Swift,[7] Bain and Hamilton,[8] Donner,[9] Bezancon and Weil[10] and Rothschild, Sacks and Libman[11]). Furthermore the *T*-wave changes were identical to those produced experimentally by F. M. Smith,[1, 2, 3] when he tied off branches of the coronary artery. We felt, therefore, warranted in our diagnosis of occlusion of the coronary artery. Embolization was ruled out by the physical examination which eliminated mitral stenosis, subacute bacterial endocarditis and thrombophlebitis, and the negative laboratory data. What interested us was the relation between the closure and the typical attacks of rheumatic fever during which this apparent closure occurred. We assumed the direct bearing of the rheumatic infection on the production of the latter.

Quite early the French mentioned changes which occur in the vessels in rheumatic fever (Hayem,[12, 13] Martin,[14, 15] Landouzy and Siredey,[16, 17] Huguenin.[18] Later Krehl[19] and Cowan[20]). In 1894, Romberg[21] described extensive hyaline thrombus formation and intimal thickening and cited also a case report of Leyden.[22]

Aschoff[23] states that all coats of small- and medium-sized arteries may be involved in the process of submiliary nodule formation. Aschoff and Tawara[24] say "aside from these last changes, healing of the arteritic and periarteritic foci can cause such sclerotic narrowing that ischemic necrosis may result. At all events we believe that all scars are due either to plugging of vessel or anemic necrosis and not primarily to interstitial myocarditis." Aschoff[25, 26] further says that this anemic necrosis plays a large part in the myocardial weakness in rheumatic fever. Giepel[27, 28] tells of the presence of giant cells in the vessel walls and the lumina of small arteries. The nodules in the arterial wall may cause a real breach due to injury of the elastica and media. He cites a case where a man suddenly died while walking and in whose heart numerous nodules were found: "On the descending ramus of the left coronary artery the entire wall was penetrated in two places by the destructive process." In 1909, he[29] describes the process as beginning at the periphery and extending inwardly. Coombs[30, 31] mentions arteritic and periarteritic processes occluding vessels, and emphasizes this in later writings,[32] and again in his book.[33] Takayasu[34] found similar changes and noted crescent formation on cross section, due to wall infiltration with new tissue showing a granular structure in which endothelial cells were embedded, giant cells present and at times thrombi seen.

These sections followed serially showed they represented a lengthwise stenosis of a portion of the artery. Wätjen[35] reported an unusual case of recurrent rheumatic infection in a man aged fifty years. The heart showed old healed scars and fresh infarcts, with nodules invading the walls of the vessels. When the nodule was not present, the wall was invaded by eosinophilic leukocytes and the lumen filled with either fresh thrombi or older organized tissue, partially or completely closing the lumen. The nodule may form in any layer of the artery and produce the clinical condition he termed arteritis nodosa rheumatica. Gerhardt[36] cites a closure of a small branch to the conducting system in rheumatic fever. MacCallum[37] says involvement of the coronary system is not very common but does occur.

Swift[38] states "changes in the bloodvessels are common. Not infrequently one encounters complete or partial closure of the lumina with thrombi that have formed as a result of injury to the vessel. The bloodvessel may be constricted in other ways. Compression may be due to nodule in the perivascular space. Endarteritis with swelling and proliferation of the endothelium is not infrequently encountered in the smaller branches of the coronary arteries. Interference with the circulation must lead immediately to disturbed nutrition of the muscle tissue and of impulse conduction." Sacks,[39] in discussing the vascular changes, quotes Libman[40] and Hess[41] who speak of thrombosis in veins as well as other arteries.

Recently, von Glahn and Pappenheimer[42] described specific lesions of the peripheral bloodvessels and in 1927 these authors[43] showed the widespread extent of the involvement of the vascular system in rheumatic fever, changes being described in the large vessels, notably the aorta, resembling the accepted rheumatic lesions, namely verrucæ and Aschoff bodies. That the intima of the large vessels such as the aorta, pulmonary, innominate and carotid arteries are frequently involved has, however, long been established, Jores,[44] Stumpf,[45] Reiche,[46] Heydloff.[47]

The review of the literature indicates that rheumatic fever frequently involves arteries of various sizes. Our interest is concerned in the specific involvement of the coronary system. The coronary arteries may be involved directly as shown by the intimal changes or indirectly by the submiliary nodule. The earliest changes are those of proliferation of the endothelial cells. They begin to heap up but are not destroyed, fibrin is deposited beneath this layer, eosinophilic leukocytes may infiltrate the wall, but more often there is a small round-cell infiltration. The size of the artery seems to determine the further course. In the aorta structures like that of the nodule or even verrucæ may form. In the coronary arteries the subendothelial deposit may so lift up the endothelium that the lumen may be completely occluded, or the heaping up of the endothelium may be localized to one side of the vessel, and there may undergo

organization producing nodularity of the lumen. If the process goes further, necrosis of the media takes place and the elastic lamina now begins to share in the process. At this stage thrombosis may take place, though the formation of a thrombus does not depend on the degree of involvement of the vessel. Why in severe involvement no thrombosis may take place; and, on the other hand, will take place with a minimal or practically noninvolvement is hard to say; that there is another factor in the production of a thrombus is certain for it occurs rather frequently in rheumatic fever.

When the coronary artery is involved indirectly, it is by way of the Aschoff nodule which begins in the perivascular space or in the adventitia. This enlarges toward the media and the first result may be compression of the lumen and resultant ischemic necrosis. The nodule may involve the media and adventitia, producing a nodularity of the lumen. It may even cause a destruction of these coats and produce a breach in the wall of the artery. As can be seen, thrombus is a likely sequel. Healing takes place by fibrosis of the intima, producing irregularity of the lumen, or, if thrombus takes place, organization of it with recanalization.

Our case had a rheumatic involvement of her myocardium for six months prior to her admission during which involvement of the wall of a large branch of the coronary occurred. Suddenly thrombosis of this vessel occurred giving rise to the picture of intense angina, as noted also by Kaufmann,[48] Mönckeberg.[49]

A consideration of the involvement of the coronary arteries in rheumatic fever suggests that the symptomatology resulting therefrom may be divided into three groups.

The first group is rare. It includes those cases in which a severe attack occurs during the course of the active stage of involvement of the myocardium in the rheumatic infection, due to involvement of one of the main branches of the coronary artery. It is due to involvement of a large branch of the coronary artery that sudden death may occur, as in the case of Giepel,[27] or thrombosis may take place, producing a severe attack of angina pectoris with recovery as in our case.

The second group includes those cases in which the symptoms are caused by the involvement of the coronary branches of small or medium size. This is the frequent or usual type. The symptoms may be of three kinds:

1. Pain. This is mild, variously described by the patients during the active stage of rheumatic fever as annoying, pinching, aching or scratching. If the vessels involved are near the pericardium, pericardial reaction and its type of pain is produced.

2. If the process is very extensive, the nutrition of the myocardium suffers and symptoms of cardiac embarrassment are produced; or, if previously present, aggravated.

3. If the nutrient vessels to the conducting system are occluded, various types of irregularity are produced.

The third group has been little emphasized and may more properly be regarded as a sequel. Healing as has been mentioned frequently takes place, producing fibrous nodularity of the lumen. This site may become the locus for arteriosclerotic processes. It is but another step for these patients to become the sufferers of angina pectoris. Patients who suffer from angina pectoris especially those of the fourth decade frequently give a history of rheumatic affection. This has recently been the subject of a paper by Kahn[50] who in 82 cases of angina pectoris was able to obtain a history of rheumatic fever in 20 and of recurrent attacks of tonsillitis in 28. This latter condition is interesting in the light of the observations of anginal attacks ensuing upon recurrent tonsilar infections and their cessation upon the removal of diseased tonsils (Louria[51]).

Summary. 1. A case of thrombosis of the coronary artery due to rheumatic disease with characteristic electrocardiographic findings is reported.

2. The symptomatology and pathogenesis of rheumatic coronary arteritis are discussed.

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THE CHANGING CLINICAL PICTURE OF LESIONS OF THE BREAST.

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The clinician or internist today is called upon more and more by his patients to make a complete physical examination, and by his most enlightened clientele an annual periodical survey. In addition to this, due to the educational effort of the medical profession in this country, the majority of women no longer delay when their attention is called to the breast by any type of warning.

Up to 1900, and even up to 1910, in the ordinary physical examination, the breast received scant attention, even the thyroid area was usually overlooked, although the presence or absence of palpable glands in the neck, axilla, groin, supratrochlear area were usually noted in the histories. When women came to surgeons referred by their family physicians, with the rarest exceptions, the breast was the seat of a perfectly definite lump. My figures show that 80 per cent were cancer, and 20 per cent benign. Of the benign group in not more than one was operation not indicated. This has changed. My most recent figures are: 17 per cent malignant; 18 per cent benign, with definite lumps which were subjected to operation; and the remaining 65 per cent benign, in which operation was not indicated.

When the per cent of malignant lumps in the breast were 80, the inoperable group was 50 per cent or more, and the five-year cures 20 or less. When the per cent of malignancy in the entire group had been reduced to 20, or in the group in which operation

was performed, to 50, the inoperable group had fallen to less than 5 per cent, and the five-year group had increased almost to 60.

In former years it was minor diagnosis, major surgery and minimum results. Today, it is major diagnosis, minor surgery and maximum results. Today the first difficult clinical problem is to find by palpation the definite lump. The next is a surgical-pathologic problem to distinguish, in the fresh frozen section made in the operating room, the benign from the malignant.

There is, therefore, much that a surgeon and surgical pathologist (who has had the good fortune to live through this long period of thirty-nine years) has to tell his colleagues about the inspection and palpation of the breast in the routine physical examination and in the periodic examination, and in the enlightened group of women who seek his advice the moment they are warned.

There is, first, the inspection of the nipple for areas of keratosis and irritation which, if neglected lead to Paget's cancer of the nipple; the interpretation of the different types of retracted nipples and discharge from the nipple. Then there are the visible swellings in the axilla which are often aberrant breast tissue; the significance of pain in one or both breasts; its relation to definite pathologic processes in the breast, to menstrual periods, and to fear. It is well known that the two breasts of an individual differ in their size. They may even hang at different levels. It is not so well known that there are various types of breasts which give to the palpating finger different sensations—the breast of pregnancy is a little different from that at puberty; the lactating breast is distinctly different, on palpation, from those at pregnancy and puberty. The change in the breast after lactation produces various pictures to be seen on inspection and changes on palpation. A very common disease of the breast, *chronic cystic mastitis*, gives rise to the bilateral *lumpy* breast or *shotty* breast, or *dilated ducts beneath the nipple*, or to definite single and multiple tumors in one or both breasts.

Enlightened women now consult us for warts, moles, angiomas, of the skin of the breast, for subcutaneous fibromas and dermoids in the breast area, for the skin reaction after mosquito and other bites, for hypertrophy of the glands of the areola. In fact, my experience with benign lesions of the breast and in the region of the breast since my publication in 1921, eight years ago, has so increased that it is not only difficult to keep up with the study of the larger numbers of cases of the same type, but to correlate the new things.

The following stand out prominently and should be emphasized: (1) The increasing percentage of benign lesions for which operation is not indicated, but which must be recognized by inspection, palpation and the interpretation of facts in the history. (2) The difficulty of convincing women with pain in one or both breasts and no definite lump, that it is not a sign of cancer. (3) The greatest difficulty of distinguishing a definite from an indefinite lump, or

recognizing a definite lump in the lumpy breast, in the shotty breast, or one mixed with the palpable dilated ducts beneath the nipple. That is, a larger number of women every year are being referred to surgeons, because one or more members of the medical profession have thought they felt a definite lump, and that operation was indicated. This is not at all a dangerous mistake. In fact, it is fortunate for both, the women and the surgeons, providing the surgeon can distinguish between the definite and indefinite lump. If not, the woman is subjected to an unnecessary operation and may even lose the breast. But she does not die from cancer.

In the next group, which is fortunately smaller, the definite lump is looked upon as a "caked" breast or mastitis, and operation is deferred until the clinical picture of malignancy is distinct, and the chances of a cure very much reduced. Now, as a matter of fact, this area of mastitis is really like the caked breast of lactation mastitis. Even the women do not call it a "lump," but speak of it as an enlargement or a glandular mass, or even a caked breast. The one or more doctors who feel the breast never overlook finding the area on palpation, but because it feels so different from the majority of tumors or lumps in the breast and so much like the caked breast of lactation, it is diagnosed mastitis, because the majority of the medical profession today have not been taught, or have not learned from experience, that cancer of the breast may, in the onset, palpate like ordinary mastitis—tubercular, pyogenic or traumatic.

I will speak of mastitis or the caked breast again. It is a very dangerous thing to delay in this type of breast lesion.

A zone of mastitis in the upper and outer quadrant of the right breast was recently palpated by my associates Drs. Stewart and Cohn and me. To all of us it felt like cancer, but there were no malignant changes in nipple, skin or subcutaneous fat. On transillumination, it was darker than the surrounding breast, but a diffuse cloudiness, not a circumscribed, dark area, as pictured and described by Max Cutler of the Memorial Hospital in New York in his article on "Transillumination of the Breast" in Surgery, Gynecology and Obstetrics.

The next day, on the operating table, I thought I elicited fluctuation in this area, but I knew that edema around a buried cancer would give pseudofluctuation of this type. The only point in favor of chronic cystic mastitis was a somewhat similar, but much smaller and indefinite area in the upper and inner quadrant of the opposite breast. At exploration, it proved to be a thick-walled cyst buried in breast tissue in which there were other, smaller, cysts, and the surrounding breast tissue showed mastitis. The breast was saved. It could have been cancer, or tuberculosis. As the patient had never had children, we could exclude lactation mastitis.

To repeat, I will emphasize areas of mastitis again, hoping to influence clinicians not to delay operation in this group.

Benign Conditions of the Female Breast for Which Operation is not Indicated. Impressed by the fact that of the last 100 female patients who had come under my observation, more than one-half belonged to the group of benign lesions for which, we had learned, operation was not necessary, in December, 1921, I presented this new phase of the breast problem. In the introduction to this present paper I have recorded the fact that in these eight years the group had increased from 50 to 65 per cent.

My records in 1921 showed 267 cases which were divided as follows: (1) Pain; (2) painful scars; (3) discharge from the nipple; (4) retraction of the nipple; (5) lesions of the nipple suggesting Paget's disease; (6) history of disappearing tumor; (7) definite and indefinite single and multiple tumors in women under twenty-five years of age; (8) definite and indefinite single and multiple tumors in women over twenty-five years of age; (9) tumors in the axilla, aberrant breast, lipoma, lymph glands, lesions of the sebaceous and sweat glands; (10) unilateral hypertrophy; (11) diffuse *virginal* hypertrophy.

These groups have been studied and restudied frequently since. We know results in practically all the cases today. The incidence of cancer seems to be about the same as in any group of women of the same age who are followed for nine years.

I am unable to give the exact number of cases today—roughly, it is more than 1000. For example, shotty breasts have increased from 3 to almost 100. Judging from the letters and personal conversations I have had since this paper was published in 1922, it impressed my colleagues in internal medicine and general practice as very helpful.

In a paper by me on the "Clinical and Pathological Diagnosis of Diseases of the Female Breast,"[2] any remarks in regard to this group are conspicuous by their absence, so that it is appropriate for me to record in this journal the experience I have gained in these years. The benign conditions of the female breast for which operation is not necessary did not become prominent until the educational program had gone on for some years and until we had learned that operation was not indicated in many clinical manifestations of chronic cystic mastitis and in discharge from the nipple without a palpable tumor, or in discharge from the nipple with palpable dilated ducts beneath the nipple, or associated with a shotty or lumpy breast. As a matter of fact, this group did not begin to be prominent until about 1919.

1. *Pain.* We have educated women now to report when they experience pain, but do not feel a lump. Before this, they rarely, if ever, reported for pain only, and rarely for lump unless there was pain or rapid growth, or ulceration.

Again and again we have grouped benign and malignant tumors of the breast which had been operated upon as follows: Tumors,

no pain; tumor, interval, then pain; pain, interval, tumor; pain and tumor observed almost simultaneously. The interesting study is how frequently does pain in the breast antedate a malignant tumor, or how often is pain the symptom of onset in cancer of the breast? How frequently do women experience pain in the breast without the later development of cancer, even over a period of years? We can answer this with considerable exactness.

In 1920, we only had 50 patients who consulted us for pain only, and in whom we could find no definite tumor. There have been at least 200 more cases since then, Therefore, pain is a frequent observation in the breasts of women who apparently run no more risks of cancer or any other operable lesion of the breast than women who have no pain. In benign tumors, pain is a more frequent symptom of onset than in malignant tumors. I can explain this only by the fact that pain is more frequent in the breasts of the younger women within the age limits of the benign lesions, and less frequent in the breasts of women at the cancer age. The pain recorded in all these histories, in the *no operation* group, with the benign tumors and in cancer of the breast, shows the same variable character before the palpation of the lump. Pain after the knowledge of the lump by the woman is of no diagnostic value. It is important to remember that many women have pain in one or both breasts, most commonly experienced just before the menstrual periods. They may have localized pain in one breast for years; it may be associated with tenderness. The conclusion we reached in 1921 is still correct—pain and tenderness are of no value in the differential diagnosis of breast lesions. The value of pain is this—if it is a symptom of onset, it may lead the patient to feel a lump if present; if there is no lump it may bring the patient for an examination which should be repeated at short intervals for at least three months and then once a year. So far, I have never found a malignant tumor in a woman who sought examination for pain only. I have a record of only one case in which a malignant tumor of the breast was discovered during an ordinary physical examination, the patient being unaware of pain in the breast. We should continue to urge women to seek an examination the moment they feel pain.

Pain and Fear of Cancer. There is no question that the basic influence which brings the majority of women under medical observation with lesions of the breast, is the fear of cancer, and I trust that we can continue to be so fortunate as to keep this fear within limits, so that it will not put off the examination. When the examination reveals no lump to be operated upon, the most important thing to do—often a very difficult thing to accomplish—is to relieve the patient of fear. Repeated examinations and conversations will accomplish this.

2. *Painful Scar.* The statements of 1921 are still correct. Pain in a scar in the region of the breast is not a sign of recurrence of the

disease for which the operation was performed. The same factors which cause pain in the scar anywhere in the human body are active in scars in the region of the breast. I have never excised a scar of the breast for pain. When the patients are relieved of their fear of cancer, they put up with the pain in the scar. In recent years I have looked for foci of infection and removed them, if present, have advised frequent hot baths in cold weather, and extra flannel or woolen covering to prevent chilling of the scar area when the thermometer is low. Pain in the scar is largely a circulatory phenomenon. Add to this the fear of some serious disease, and the patient comes under the observation of the medical profession.

3. *Discharge from the Nipple.* I still hold to the opinion expressed in 1921 that discharge from the nipple, no matter what its character, is not a sign of cancer. We have made the same study of discharge from the nipple as we have made of pain, with practically the same conclusions. The number of cases we had observed to 1921 in which operation has not been performed, has now increased to more than 100. We have found that discharge from the nipple is observed in about 1 per cent of all groups of breast tumors—benign, malignant and "no operation." This is about the incidence one would find of cancer. The causes of discharge from the nipple are, first and most frequently, a papilloma in a duct. Here the character of the discharge is hemorrhagic or serous. In galactocele and in residual lactation hypertrophy it is like milk or cream. In dilated ducts beneath the nipple which may accompany chronic cystic mastitis, the discharge is not bloody nor serous. It is usually grumous and may be yellow, brown or green.

Discharge of blood from the nipple has been most frequently observed in a group of benign tumors called intracystic papilloma. The incidence of such discharge is recorded in about 50 per cent of the cases. It may be a symptom of onset and may be present years before the tumor is felt and removed. It may be observed simultaneously with the palpation of the tumor, or at intervals after the tumor has been felt. *We have not a single record of cancer of the breast developing in a papillomatous cyst,* unless the palpable tumor has been observed nine months or longer. I have no evidence that a woman who has a discharge from one or both nipples, and whose breasts, on palpation, are found free from tumors, runs any more risk of cancer than a woman who has pain and no palpable tumor, or any female who has neither. As Osler would say, the patient with pain in the breast, or discharge from the nipple should run less risk of cancer, because such symptoms should lead to more frequent examinations.

A small per cent—less than 10—of the patients who consulted the clinic for bloody or serous discharge from the nipple and at whose first and subsequent examinations no lump was felt, have developed

a lump months or years later, and this lump has been removed, and proved to be papillomatous cyst, and the breast has been saved.

In the majority of these patients ultimately, after years, the discharge ceases.

Today, for the first time, I operated upon a patient of mine who had observed a serous or bloody discharge from the right nipple at intervals over a period of nine years. She is now over fifty and has passed the menopause. At no examination had we been able to palpate a tumor. She has reported by letter at intervals of every six months during these nine years. She has been examined at least once a year by her family physician and less frequently at the clinic. The patient returned because, after an interval of about three years in which no discharge was seen, it has now reappeared and is bloody. There is no tumor to be felt. There is a small dark spot beneath the left discharging nipple, not seen beneath the right, on transillumination. The left discharging nipple is larger than the right, yet there is no keratosis, no signs of irritation suggesting beginning Paget's disease. As I have recently learned how to excise the nipple and a zone of breast beneath it in the benign stage of Paget's disease of the nipple, or for infected dilated ducts beneath the nipple simulating, clinically, early malignancy, I decided that this patient had better be relieved of the mentally annoying discharge, and malignancy absolutely excluded. Under procain, we removed the nipple with a small zone of skin including the areola, and a zone of breast beneath. As we cut through the breast tissue, we encountered no dilated ducts or cysts. Frozen sections from this breast tissue showed adenomatous areas and one small zone of papillary cystadenoma which is quite a common occurrence in a breast the seat of one or more papillomatous cysts within the ducts. After we had removed the mass and bisected it through the nipple, there was exposed a somewhat long, bottle-shaped, light-brownish mass, beginning 5 mm. beneath the nipple, about 8 mm. long, and 3 mm. in width. It had a distinct cyst wall and, on section, was filled with a grayish, friable papilloma. Sections showed a benign papilloma of the duct. There was no evidence of malignancy in any of the frozen sections. The patient was saved the mutilation of the removal of the breast.

During the same week another patient came under my observation with the recurrence of a discharge from the nipple after its first appearance seven years ago and after its last appearance two years ago. The question is, what are we to do for this group when the discharge persists for years, or recurs after years of quiescence? Will transillumination really help us in this group, as suggested by Max Cutler? Which is the best procedure—the excision of a zone of breast beneath the nipple, without the nipple, or with the nipple? I have performed both. It is a point to be settled by a restudy of this now very much larger group, but I can record here again that

no patient has, as yet, in our records, developed cancer of the breast, because we refused to explore the breast for discharge from the nipple.

4. *Retraction of the Nipple.* We have learned, since[3] 1922, that intermittent retraction of one or both nipples is not a sign of malignancy, but of chronic cystic mastitis, usually of the Schimmelbusch type, or the shotty breast. I brought this out in 1921.[4]

It is well understood that retraction of the nipple of the congenital type, or of long duration, dating back to an old mastitis, is not a sign of cancer. But when one nipple has recently become retracted, whether a lump can be felt or not, cancer must be suspected, and, in my opinion, the breast should be explored. But this retraction may be due to chronic cystic mastitis. Retraction of the nipple of the malignant type has been observed now and then in every type of benign lesion of the breast, less frequently in encapsulated adenoma, a little more frequently in chronic cystic mastitis (3 per cent), much more frequently in lactation and tubercular mastitis, and, of course, most frequently in malignant disease of all types. The nearer the small palpable lump is to the nipple, the less reliance can be placed on retraction of the nipple as a sign of cancer. In demonstrating the presence or absence of retraction of the nipple, not only inspect, but move both arms up over the head and watch both nipples; pull the nipple forward, to see if one is more fixed than the other. The earlier we palpate a tumor of the breast after it is first felt by the patient, the more will we depend for diagnosis on exploration and frozen section, than upon retraction of the nipple, slight dimpling of the skin and atrophy of the subcutaneous fat. Regard, however, retraction of the nipple as a sign of malignancy, until there is positive proof that there is not cancer.

5. *Lesions of the Nipple Suggesting Paget's Disease.* In March, 1921, I had observed 3 cases of irritation of the nipple which healed under the treatment with cleansing, twice a day, with soap and water, using cotton and followed by medicated alcohol; then covering the affected nipple with vaselin and a piece of gauze fixed with adhesive straps. In 1924, I[5] made a report on my entire experience with Paget's disease of the nipple. The 3 nonoperative cases had increased in three years to 7. The number now is more than 50. In 1924, 15 benign lesions of the nipple had been subjected to operation. In many the breast was unnecessarily sacrificed. Since the paper was written in 1924, and from the studies of the cases reported we now, when the simple treatment fails to heal the irritation of the nipple, excise it with the areola and a zone of breast beneath. If frozen sections reveal no evidence of malignancy, the breast is saved. If Paget's cancer is present, the complete operation for cancer is performed. Today we rarely see Paget's cancer of the nipple that can be diagnosed clinically. The majority of cases of irritation of the nipple heal under cleanliness and protection. There

is sufficient evidence to state that a neglected irritation of the nipple in a woman at the cancer age, has the same etiologic relation to cancer, as a neglected irritation of the nipple in a nursing mother has to an abscessed breast or lactation mastitis. Our studies show that prenatal care and the care of the nipple during the nursing of the child, have reduced mastitis abscess from more than 20 to less than 1 per cent. The educational program is bringing women with irritation of the nipple before the cancer stage. In every physical examination the nipples should be inspected for warts, keratosis and any form of irritation, and if these are present there should be immediate treatment. If this treatment fails in three weeks, the exploratory operation just described should be performed. I have no evidence that the congenital retracted nipple is more frequently affected with Paget's disease than the normal, but we have observed Paget's cancer in a congenitally retracted nipple. Therefore, it should receive the same inspection and the same treatment.

6. *History of Disappearing Tumor.* This is now established, with the exception of the caked breast and the lactation mastitis, which does not go on to suppuration, as a definite sign of chronic cystic mastitis. When patients observe any type of swelling or tumor or mass to vary in size, to entirely disappear, and then reappear in the same spot or in another area of the same breast, or in the opposite breast, we can safely conclude that the chances are that both breasts are involved in chronic cystic mastitis. But it does not exclude malignant disease, or other types of benign tumors. In all diseases of the breast other than chronic cystic mastitis the history of disappearing tumor has been recorded in 1 to 2 per cent of the cases; in chronic cystic mastitis in almost 20 per cent of the cases. When the palpable single tumor is the one that the patient has observed to show changes in size, or to have disappeared to reappear, this, of itself, suggests a benign cyst. If, in addition, the tumor is spherical, fluctuates and transilluminates clear, we have the almost certain diagnosis of a benign cyst. If, in addition, both breasts are lumpy, or shotty, or there are other, smaller similar tumors, the clinical picture of chronic cystic mastitis is established.

Tumor or Tumors in the Breast. Now that more and more women are presenting themselves for examination within a month of the first warning, we are palpating more and more frequently lumpy breasts, shotty breasts, dilated ducts beneath one or both nipples, multiple definite and indefinite tumors. That is, clinical manifestations of chronic cystic mastitis which is a disease like osteitis fibrosa of bone, in the majority of cases subside almost as quickly as they appear, so that after a few months' duration they are less and less frequently observed on palpation, although present microscopically.

There is another reason why, on palpation of the breast, we have to pay more attention to the entire breast and to both breasts.

This is due to the fact that when women have delayed months or years after feeling a lump, and the lump has not disappeared, the single lump is so definite that, with rare exceptions, the clinician occupies his full time in feeling this lump and recording its characteristics, and no attention is paid to the remainder of the breast and often there is no record of palapation of the other breast. During this period, as I have already stated, 80 per cent of the lumps were malignant and 50 per cent of these in the hopeless stage of cancer, while today the definite palpable, single lumps are about 35 per cent instead of 99 per cent, and one-half of them are benign.

Unless one had many opportunities to palpate the breasts of women in the earliest stage of all the lesions of the breast, one will not appreciate the difficulty of differentiation.

I have learned to divide breast tumors clinically into two great groups—those in which the patient is twenty-five years of age or younger, in which we need not think of malignant disease, and those in which the patient is twenty-five years of age or older, in which we must think of malignant disease.

For record in the history and on the index card, the letter (a) indicates a single definite tumor, (b) a definite tumor in both breasts, (c) two or more tumors in one breast, and (d) two or more tumors in both breasts. The letter (e) indicates a single indefinite area in one breast, (be, ce, de) designate multiple indefinite areas. Out of this classification there have arisen three definite types that may be composed of definite or indefinite lumps, or a combination of both—the shotty breast, the lumpy breast, and the dilated ducts beneath the nipple.

The first, most important new facts is the frequency, in the past few years, with which we may see a patient with a single lump difficult to class as definite or indefinite. If this single lump is the palpable area in either breast, it should be explored. The chances of its being malignant are almost 25 per cent, while the probabilities of malignancy in the perfectly definite lump are 50 per cent. As cancer may occur in the shotty breast, the lumpy breast, or in the area beneath the nipple in which there are dilated ducts, it is becoming more and more a triumph of tactile sensation to pick out the possible malignant tumor in these breasts filled with manifestations of chronic cystic mastitis.

We may state here that in the great majority of the cases in which the breast is the seat of a malignant tumor, there is no difficulty whatever to palpate it as a single mass. Cancer is very infrequent in the shotty breast or the lumpy breast, or when the ducts beneath the nipple are dilated.

7. *Tumor or Tumors in Woman Under the Age of Twenty-five.* It makes very little difference, if the patient is under twenty, whether the tumor is single or multiple, indefinite or definite, whether it involves one or both breasts, or is an area of mastitis

or is not. The nipple may be retracted or irritated, or there may be discharge from the nipple. Operation may be postponed, unless the tumor grows larger, or there are signs of an abscess. The indication for operation is to save the breast, and not to save the life of the patient. The most frequent tumor in women under the age of twenty-five years is an encapsulated adenoma which may be single or multiple.[6] We must bear in mind that these encapsulated adenomas may be situated outside of the breast zone and may grow more rapidly than the breast at puberty, be diagnosed incorrectly as malignant, and the breast sacrificed when removing the tumor. Aberrant encapsulated fibroadenomas are not infrequently observed in young women. In former years when all females delayed after palpating a lump, we frequently observed large tumors of the breast. The majority were sarcomas which had developed in a neglected intracanalicular myxoma.

The possibility of an aberrant adenoma growing rapidly and of the intracanalicular myxoma becoming sarcoma after a certain enlargement, is the chief reason for removal of a tumor near, or in, the breast of any female under twenty years of age, when there is any sign of growth. After the age of twenty, all palpable tumors in, or near, the breast should be removed. Left alone, they may complicate pregnancy or lactation, or later in life develop into cancer, and —very interesting to record here—these little tumors of ten years' duration or longer which are now being excised by surgeons simply because the woman has just learned that it is dangerous to leave a lump alone, are being diagnosed by pathologists as cancer. Two such cases have recently been referred to me.

These old encapsulated adenomas of any type become very fibrous and, in some instances, may even calcify; the basement membrane beneath the epithelial cells of the old parenchyma is frequently absent; masses of old epithelial cells in solid clumps, or papillomatous masses are surrounded by fibrous stroma—the gross histologic picture of cancer, but the individual epithelial cells are not, morphologically, cancer cells. It is, therefore, safer to have these little encapsulated adenomas removed before the young female passes into the cancer age and before circulatory changes obscure the microscopic picture. I have called attention before to the frequency with which all types of encapsulated adenomas have been diagnosed, by a certain number of pathologists, cancer, but I have never before called attention to this new danger of leaving a quiescent lump in the breast of a young woman alone for the fear that later in life it may be removed and diagnosed cancer, and the breast sacrificed.

All obstetricians are familiar with the enlargement of both breasts in the newborn child and the copious discharge from the nipple. The etiologic factors are unknown. It apparently has no relation to diseases of the breast later in life. If the breasts are kept scrupulously

clean and infection avoided, these breasts never give trouble. Tumors in and about the breasts of children are rare. If they are not directly in the breast, it is, on the whole, safer to remove them, even when they do not exhibit growth, because sarcoma is very common in the young.

At puberty, unilateral hypertrophy of one breast is not rare. There should be no difficulty in excluding tumor, unless the breast gets very large, when one should suspect a central adenoma which can be found and removed by exploration, and the breast saved. As a rule, very quickly, the other breast develops and catches up. Diffuse virginal hypertrophy is a bilateral disease. Its cause is unknown. We know of no way of arresting it. It is my rule, when this hypertrophy reaches a certain size, to perform a plastic operation, removing one or more wedge-shaped segments. I had only one opportunity to practise it—it was successful. Lesser degrees of diffuse virginal hypertrophy are getting more and more common in this "no operation" group. This type of breast, in its diseases, does not differ from the normal breast, but in its function, it differs distinctly. Often there is no milk, or, if any, it is scanty. It is one of the rarest occurrences in this country to see a diffuse virginal hypertrophy reach the size recorded by G. B. Johnson[7] of Richmond, Virginia, in 1903.

8. *Tumor or Tumors in Women Over the Age of Twenty-five. Shotty Breast.* I[8] described the clinical and pathologic picture of 13 such cases among 350 examples of chronic cystic mastitis, and called it diffuse nonencapsulated cystic adenoma, or papillary cystadenoma. It was first described by Schimmelbusch and Réclus in 1906, I[9] employed the term senile parenchymatous hypertrophy. The 13 cases described in 1921 were all operated upon, either the complete operation for cancer, or the removal of one or both breasts was done, in order to protect the patient from cancer. The earlier cases subjected to the complete operation for cancer were diagnosed adenocarcinoma in diffuse papillary cystadenoma; the later cases were called benign papillary cystadenoma. Within a year, I[10] employed the term "shotty" breast and described 6 cases in which operation was not performed; the earliest in April, 1921.

Since then we have records of more than 100 cases, not subjected to operation, which have been followed, and in these breasts cancer has not developed. The longest observation is eight years. During the same period 34 patients have been subjected to operation, either partial removal of a zone of the breast, or of the entire breast, or the cancer operation, but all were finally diagnosed as microscopically benign. In 3 instances, a palpable nodule distinct in a shotty breast had been explored, recognized as cancer in the frozen section, and the patients subjected to the complete operation. Shotty breasts, therefore, are now a common clinical finding. With the rarest exceptions, operation is not indicated. In a few there must

be exploration for frozen sections to ascertain if malignancy is present in an area or a tumor which can be palpated distinctly in a shotty breast. A paper on this form of chronic cystic mastitis will be soon published in detail.[11]

There is nothing distinctive on inspection. There may be a little discharge of grumous material from the nipple. The shotty breasts are practically always bilateral, although the degree may be more marked in one breast. These patients have rarely much subcutaneous fat, the majority are underweight. The breasts are rarely large. We never observe the shotty breast, the diffuse nonencapsulated papillary cystadenoma in large fatty breasts. Either the breasts have never lactated, or it is some years since the last lactation. It is practically never seen after the menopause. When one palpates the upper and outer quadrants of both breasts, one will think at once of the breasts at puberty or pregnancy. The parenchyma is distinct, and as a rule it is filled with minute shotty masses. The further development is a distinct edge like the edge of the liver, and, still further, the breast can be lifted up, like a saucer, and it then assumes its shape. This condition may involve a quadrant, a hemisphere, or the entire breast. Often one or both breasts are painful or tender, and this pain and tenderness are most marked just previous to the menstrual period.

Not infrequently one can palpate one or more larger tumors or masses in one or both breasts, which as a rule feel like minute cysts. We have only practised transillumination the past six months. The shotty breast is not as translucent as the fatty senile breast, but there were no dark areas in those that we have transilluminated up to date. The cases that have been subjected to operation, have been those in which we could palpate a single tumor that suggested the possibility of malignancy, or because the breast felt more indurated or less shotty.

There is not so much difficulty, on palpation, in picking out the group among the shotty breasts that should be explored, but there will be great difficulty in interpreting the microscopic frozen section, unless one is familiar with the various histologic changes in chronic cystic mastitis. I have pictured them in the *Archives of Surgery* for November, 1921, in Figs. 32 to 91. These pictures are just as good today as when published and practically no new pictures have been encountered. I recommend to pathologists in the operating room the study of these pictures, and I suggest to clinicians, when they have this type of case subjected to operation, to have this volume of the Archives present for reference.

Dilated Ducts Beneath the Nipple. We have been slow in recognizing this variety of chronic cystic mastitis as a definite clinical entity. In 1921,[3] I had 22 cases; in 1923[12] I was able to report seven examples of the so-called varicocele tumor of the breast which had been observed since 1921. There have been at least 60 cases since

then that have not been operated upon. As a rule, women with dilated ducts beneath the nipple are older than the group of women with shotty breasts, they are approaching the menopause. They are apt to be overweight, while the patients whose breasts are the seat of diffuse papillary cystadenoma are underweight. The condition is usually bilateral, if carefully examined. The patient's attention to the breast is attracted more frequently by pain and tenderness than by a lump, and least frequently by discharge of thick, grumous material from the nipple. On palpation, one feels

FIG. 1.—Hopeless cancer of the left breast. Patient absolutely ignorant of her condition; has no fear or discomfort. Came to the clinic because of cough and bloody expectoration. The patient lives in a locality in the country where few, if any, messages from the outside world are received or read. This is the type of cancer described by Billroth, Velpeau and Paget.

beneath the nipple and areolar zone one or more masses, usually in the shape of worms and often not larger than the largest angle worm. Each dilated duct palpates distinctly, because there is very little subcutaneous fat here. Usually the palpable tumor is not tender. Now and then pressure on the dilated duct brings forth pastille material from one or more ducts. Once felt, it cannot be mistaken in this stage, and for this stage there is no indication for operation. But the duct may become infected. If the infection is acute there will be a rapid development of a typical abscess which can be opened and drained like any other abscess. But more fre-

quently the infection is chronic, and the inflammatory reaction around the duct palpates like a possible malignant tumor, and the nipple may be slightly fixed and retracted. It is my rule to explore such cases and decide from the gross and frozen-section appearance whether it is malignant. There should not be much difficulty, as shown in the illustrations reproduced in the *Archives of Surgery*.

Dilatation of the ducts beneath the nipple may be present in any breast of a woman approaching menopause or later in life. When we look over the gross notes on cancer of the breast, we find dilatation of the ducts distinctly more frequent than cysts, or the Schimmelbusch type of chronic cystic mastitis. But I have not a single instance of a definite cancer beneath the nipple surrounded by dilated ducts. Cancer situated in the nipple and areolar zone is relatively infrequent.

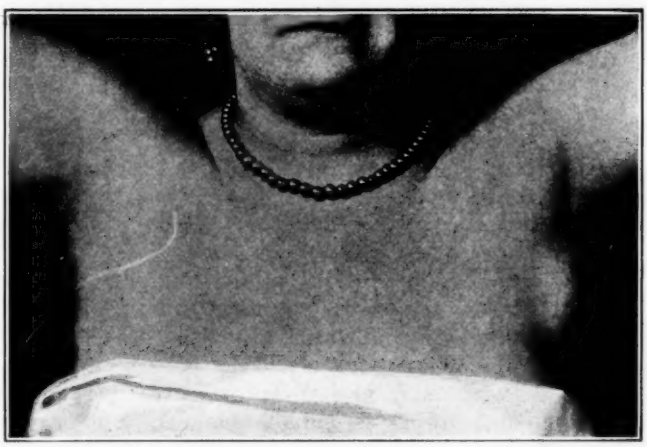

FIG. 2.—Photograph of an enlightened woman who has recently observed a lump in the left axilla. It was diagnosed aberrant breast tissue. Operation was not performed. There has been no trouble during a period of four years since. Enlightened women in this group have only 17 per cent chances that their lesion is cancer, and, if cancer, 60 per cent chances of a cure.

With this clinical knowledge, one should be able to recognize tumors beneath the nipple of the dilated-duct type, and save most patients from operation. But when infection has changed the clinical appearance, one must differentiate by excising the zone of breast beneath the nipple, in some cases with the nipple, as already described for Paget's disease, and decide as to the presence or absence of malignancy. Remember that the gross findings of dilated ducts filled with grumous material is against cancer, also that the frozen section may be difficult to interpret, because the periductal lymphoid granulation tissue will destroy the basement membrane and basal cells of the duct and the rapidly proliferating epithelial cells

of the duct will be found growing in this granulation tissue, simulating cancer. See Fig. 6, page 509, in the *Archives of Surgery* (*loc. cit.*).

Lumpy Breast. Warren, of Boston, described them as "cobblestone" breasts, and the Warren incision was devised in order to expose even a hemisphere of the breast and to remove by posterior excision one or more of the palpable masses which as a rule are not cysts. Sir G. Lenthal Cheatle, of London, in his excellent contributions to chronic cystic mastitis, has called attention to these lumpy breasts. In 1921, in 350 cases of chronic cystic mastitis, I found that there were 76 examples of this type, and most of these patients had lost one or both breasts, or had been subjected to the complete

FIG. 3.—Paget's disease of the nipple in the stage of superficial ulceration. In this case excision of the nipple, frozen sections showed cancer, and the complete operation for cancer was done.

operation for cancer. Since then I have never operated in cases of this kind unless there was a single tumor either distinctly palpable, or sufficiently different to justify exploration and frozen sections. In the past eight years I have records of at least 200 cases not operated on, but I find that in the laboratory 87 examples have been referred there for diagnosis. In many, the exploration had been unnecessary, and in every instance the removal of one or both breasts was not indicated by either the clinical or pathologic picture. When 35 per cent of women who seek the advice of a clinic after a warning of trouble with the breast have definite tumors, on palpation, and 65 have not, bilateral lumpy breasts are by far the most common finding. Yet my laboratory records now 163 speci-

mens of this condition received from different sources. In not more than 40 of these was exploration justifiable.

The majority of lumpy breasts are due to chronic cystic mastitis scattered in areas throughout the breast. These areas are not unlike areas of nonencapsulated adenoma, and, microscopically, they may resemble fibroadenoma, cystic adenoma and—rarely—intracanalicular fibroadenoma. In a number of instances the nodules are due to one or more minute cysts or dilated ducts. With the rarest exceptions, the multiple cysts, like the single cyst, palpate like definite tumors. Multiple lipomas may produce a lumpy breast. Sometimes the senile breast is distinctly lumpy due to irregularities in the distribution of fat and fibrous breast stroma. The lactating breast may be lumpy, and for some years after the last lactation, the breast may remain lumpy. In some instances, these lumps are due to residual areas of lactation hypertrophy. I have found such areas fourteen years after the last lactation.

In a few instances, when the upper and outer quadrant of the breast is shotty, the lower hemisphere is lumpy. Distinct cysts palpating like single or multiple tumors are more frequently found in lumpy breasts than in shotty breasts. Distinct dilated ducts beneath one or both nipples are found in shotty breasts only rarely, but frequently in the lumpy breast. Single and multiple cysts often accompany dilated ducts beneath the nipple.

In brief, all the clinical pictures, on palpation of one or both breasts, are associated with definite pathologic changes, and the most common factor in these is chronic cystic mastitis.

No one can diagnose breast lesions safely today without familiarity with the clinical and pathologic pictures of chronic cystic mastitis.

Multiple Definite Lumps in One or Both Breasts. In younger women the most common finding is encapsulated adenoma; in older women some pathologic variety or stage of chronic cystic mastitis. Rarely is cancer found when the breast is the seat of multiple areas of chronic cystic mastitis or adenoma. Rarely is cancer a multiple tumor in one breast, and when such is observed, the other malignant areas are metastatic. Very rarely does cancer appear simultaneously in both breasts. As a rule benign multiple lesions are bilateral, malignant unilateral. Too many breasts of older women are sacrificed because of multiple blue-domed cysts, which is a perfectly distinct clinical picture. I reported 28 cases in 1921, and find 14 more in 1929, a total of 42 cases.

Areas of Mastitis or Caked Breast. My associate, Dr. L. Clarence Cohn, has been going over this subject for some years, and his paper is almost ready for publication. In the *Boston Medical and Surgical Journal* (*loc. cit.*) I presented, with illustrations, diffuse mastitis, lactation mastitis, tubercular mastitis, nonlactation mastitis, comedo-adenocarcinoma diffusely involving the breast with the clinical picture of mastitis, and carcinoma mastitis. I have already dis-

cussed this clinical picture and described a recent case in which a zone, almost a hemisphere of the breast, was the seat of a mass which palpated like mastitis. At exploration, it was due to multiple cysts buried in breast tissue. So we must add to the types described in 1922 the fact that chronic cystic mastitis of the cystic variety may produce a tumor of the diffuse mastitis type. We have already emphasized that the shotty breast simulates mastitis, but has, in addition, multiple shotlike areas and may develop a saucer-shaped palpable mass. Recently, I operated on a woman with cancer mastitis that had reported to her medical adviser the moment she felt the indefinite lump in her breast, and this patient has been under observation and treatment for six months with the diagnosis of mastitis. She had been treated with sunlight and violet rays. As the mass became larger and the nipple fixed, suspicion of malignancy urged them to refer the patient to a surgeon.

There is nothing more insidious than the type of cancer that produces an area of induration like a caked breast. There are really only two types of mastitis in which delay is justifiable—one, the pregnant or lactating breast with fever and leukocytosis and clinical evidence of inflammation. The other is the typical shotty breast, which is bilateral. But when the shotty breast presents a diffuse, hard zone, without the multiple shotlike areas, one must explore. As I am writing this for clinicians and not surgeons or pathologists, I believe I will accomplish better results by saying no more, except—*Do not delay when the mass in the breast of a woman over twenty-five suggests mastitis on palpation.*

9. *Aberrant Breast Tissue in the Axilla.* In 1921, I had notes on 17 cases—14 unilateral, 3 bilateral. The number now has increased to about 50 cases. Cancer in breast tissue in the axilla has occurred in about 3 per cent of the cases. The patient's attention to aberrant breast in the axilla is attracted by seeing or feeling a mass there which is quite prominent on inspection, and palpates like breast tissue. Now and then this mass proves to be entirely composed of fat. So far I have never observed chronic cystic mastitis in aberrant breast tissue, although this tissue does enlarge during pregnancy and lactation. In none of my cases have there been nipples in these axillary masses of breast tissue. Operation is not indicated, unless one can palpate a definite tumor, or unless the mass gets large enough to justify its removal.

Sebaceous and Sweat-gland Nodules in the Axilla. Their chief interest has been in patients upon whom the complete operation for cancer has been performed, months or a few years previous to the appearance of these single or multiple nodules in the hair zone of the axilla. In all of the cases of which I have records, the diagnosis of recurrence has been made, and many of the patients were subjected to irradiation. These tumors are, clinically, definitely inflammatory. Excision and frozen section will confirm the diagnosis. It is unnecessary to remove them to accomplish a cure.

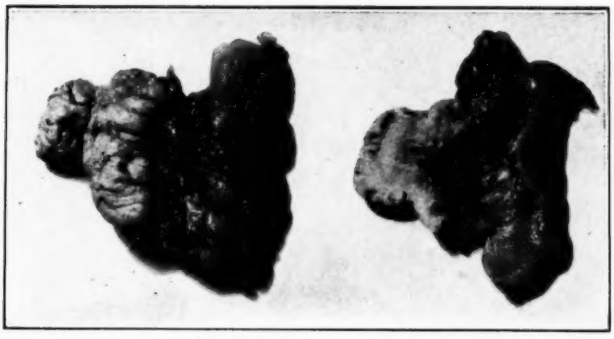

FIG. 4.—The excised nipple in an earlier stage than in Fig. 3. The frozen sections showed cancer. Complete operation was performed.

FIG. 5.—Pathol. No. 25560. Photograph of a typical blue-domed cyst buried in senile fatty breast.

FIG. 6.—Pathol. No. 10940. Photograph of a bisected blue-domed cyst removed with a zone of breast tissue. Note the thin, smooth wall of the cyst. The surrounding breast is a mixture of fat, elevated gray dots of adenomatous areas, and one minute cyst.

FIG. 7.—Pathol. No. 37068. Photograph of an encapsulated adenoma. Surrounding breast is adenomatous. This adenoma proved to be a solid intracystic papillary adenoma.

10. *Unilateral Hypertrophy at Puberty.* I have already referred to this; unilateral hypertrophy at later ages, with the rarest exceptions, means some form of encapsulated adenoma, and if the mass is larger than a quadrant, beware of sarcoma.

It is interesting to note that in the male the diffuse hypertrophy begins in one breast; in from three to six months later it appears in the other breast, and, if left alone, will disappear in a few months. Cancer of the breast in the male is insidious, and fully developed clinically it is usually hopeless. For this reason, when a man comes under observation with an enlargement of one breast of a few weeks' duration, it is best to excise the whole area with the pectoral fascia under local anesthesia and exclude malignancy by frozen sections. If the lesion is benign, you should prepare the patient and his physician for the subsequent enlargement of the other breast which may be left alone.

11. *Diffuse Virginal Hypertrophy.* This has been discussed, and there is nothing to add, except one very remarkable pathologic finding which demonstrates that benign pathologic processes may resemble closely malignant ones.

Through the courtesy of Dr. Johnson (*loc. cit.*) I was able to study the lesions of his case. On cross-section through the huge breast (Fig. 4) the hypertrophied breast tissue had destroyed all the subcutaneous fat by pressure or infiltration, and lobules of breast parenchyma were found directly beneath the corium.

New Benign Lesions of the Breast for Which Operation is not Indicated. I find that since my article in 1921, a number of patients have come under observation and have been placed in this "no operation" group whose lesions cannot be classified under the 11 headings just discussed.

12. *Changes in the Breast the Result of Atrophy After Lactation.* When the patient is in the proper position for inspection and palpation, that is reclining on her back with her arms over her head, one may observe that the nipples fall into a depression in the breast which can be palpated almost like a crater, and the areola and skin around the nipple are thrown into wrinkles. This is usually present in women who have nursed one or more children and the condition may persist throughout life. It is not a sign of cancer. It usually disappears when the woman sits up or places the arms to her side when she is lying down.[13]

It is important to bear these changes in mind, because this picture of the nipple and skin might suggest malignancy.

13. *Skin Lesions of the Areola and Skin Over the Breast.* These should be treated just the same as skin lesions elsewhere in the body. Elevated pigmented moles and warts should be removed. But every now and then one may feel in the skin of the breast a nodule, not unlike the skin metastasis from a cancer of the breast. In a very few instances a skin metastatic nodule may be the first sign of cancer

of the breast. The microscopic study of such a nodule after removal, will differentiate it.

The little skin dermoids always have a pucker or dimple on top and if they were buried in the breast, would suggest malignancy. On the whole, it is safer to remove them. There have been a number of cases of insect bites which produce a skin nodule similar to that following the injection of fluid into the skin. There may be a red area around it. Now and then erysipelas develops. Less frequently beneath it, an inflammatory reaction takes place giving rise to a tumor or mass which palpates like malignancy or mastitis.

The Proper Position for Examination of the Breast. Since my description of this, with illustrations, in 1921, there are only two new statements. The most important is the transillumination, as described by Max Cutler.[11] This additional aid has been employed in my clinic in every case for a number of months. In the roentgenological department of the Medical School in Rochester (N. Y.) they are making Roentgen ray plates of the breast, trying to picture the soft part lesion, as they would a lesion of bone. Transillumination is quicker, but the Roentgen ray leaves a more accurate record. I would advise against depending upon these procedures until one has gained considerable verified experience.

The patient should be stripped to the waist and so prepared that the abdomen can be palpated. She should recline on a couch or examining table, on her back, chest and head slightly elevated. The fingers of both hands should interlock over the head. The examiner should not know which breast is involved until inspection, palpation, and transillumination are completed. On inspection, first look carefully at the nipples. Any keratosis or irritation of the nipple should receive immediate attention, and the patient then and there instructed how to treat it. Do not touch the nipple or areolar area until the last. Look for axillary masses and the thyroid area. Note the changes which you can see in the nipple and the skin around it. On palpating use both hands first, feeling similar areas of both breasts at the same time. Use your fingers as you would when playing the piano. Do not grasp the breast tissue and pick it up—it will give you a wrong impression. Pass the fingers of the hand a number of times around the periphery of the breast and into the axilla, and palpate as you would playing the piano. At once you can distinguish the shotty breast and the lumpy breast. At once you can tell whether there is an edge to the area of involved breast. Then you can lift up the edge and see if it is saucer-shaped. Now palpate the mid zone in the same way. At any moment you may feel one or more definite tumors. Leave them alone temporarily and go on with your examination of both breasts. Now palpate the areolar area for dilated ducts. As a rule this may induce an apparently retracted nipple to become prominent. The last thing to do is to pull on the nipple to see if it is fixed. Now make a diagram of both breasts and record the position

of definitely palpable lumps by circles showing their size and position. Write the word "shotty" or "lumpy" in the area in which you have found these conditions, and the words "edge" and "saucer" if this is brought out by palpation. Write the letters (dd) near the nipple if you find dilated ducts. Now move the arms from their elevated position down to the sides of the body, one or both, and note whether one breast or nipple is more influenced by this motion of the arms than the other. Recent experience has convinced me that we must not put too much reliance on differences brought out by this maneuver, unless it is very marked it is of no value. Now palpate the single lump, get its movability, does it fluctuate; does the skin over it dimple when it is pushed forward; is the subcutaneous fat between the tumor and the skin atrophied; what does the tumor feel like; is it spherical like a cyst, lobular like an adenoma, infiltrating like cancer, or is it an area of mastitis? How does the breast palpate around the lump? Are there other definite lumps?

Then ask the patient what she has felt. All doubtful cases should be examined again the next day, and some cases should have repeated examinations within the next few months if it is decided that operation is not indicated.

Shall we postpone operation if there is a single definite tumor in one breast which palpates like a spherical cyst and fluctuates, and transilluminates clear, and when this and the other breast are otherwise normal? I am beginning to do this in a few instances. Unless you have had considerable experience this postponing the operation may be dangerous. However, if, in addition, there is a definite history of change in size or even disappearance, and both breasts are lumpy, delay is less dangerous. If there are definite multiple tumors, there is no danger in delay.

In all other types of a definite single tumor in women over twenty-five years of age, any delay is unjustifiable, and there is no way, clinically, of distinguishing the benign from the malignant. It is also safer that such a patient should be operated on in a hospital where the surgeon is prepared to make and interpret frozen sections during the operation.

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SECONDARY ANEMIA IN PREGNANCY AND IN PUERPERIUM.

A Study of Three Hundred Patients.

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The exact nature and course of secondary anemia affecting the gravid woman is not well understood. For this reason, the present study of the subject of anemia in pregnancy and in puerperium has been undertaken.

Blood examinations, made in 300 women in the various periods of gestation and in the puerperium, form the basis of this communication. A special effort was made to determine, if possible, the relationship of the existing anemia to the various associated maternal conditions.

An analysis of the red blood cell counts and hemoglobin determinations in 200 dispensary maternity patients and 100 private patients is presented in the accompanying tables and figures.

Routine hematologic examinations have been made in all patients registering at the prenatal clinic since March, 1928, the examinations consisting of erythrocyte and leukocyte counts, differential counts, hemoglobin estimations, Wassermann tests, and blood sedimentation tests.

The first count was made at registration of the patient, the second within forty-eight hours of delivery, and a third count five to eight days later. Additional counts were performed at term in a number of ward patients. The examinations of the private patients were made a few days to a few hours before delivery.

The ward patients were chiefly of the poorer classes, and were more or less undernourished. None of the patients studied suffered from any acute infectious disease or from any complication with hemorrhage during pregnancy.

All the blood examinations were made by one qualified technician who devoted his entire time to this work. The Thoma hemacytometer, with the Leitz counting chamber supplied with the Neubauer

ruling, was used for cell counting. The percentage of hemoglobin was determined with the Dare hemoglobinometer. This instrument was selected, because it is easily read and sufficiently accurate for the purpose of this study. In this method 13.8 gm. of hemoglobin per 100 cc. of blood is regarded as 100 per cent. In 100 women between the ages of eighteen and thirty years, Osgood and Haskins[40] found the average hemoglobin content to be 13.69 gm. per 100 cc. of blood, practically the same figures as those on which the Dare instrument is based.

Historical Review.—Anemia complicating pregnancy has been the subject of numerous investigations since Nasse,[38,39] in 1836, first stated that the number of red blood cells was reduced in the pregnant woman and spoke of the "anæmisierenden" influence of pregnancy. Much better known than the secondary or so-called physiologic anemia of pregnancy which is the chief consideration of this paper are: (1) The pernicious type described by Channing[12] in 1842, and, (2) the severe form of hemolytic anemia reported by Rowland,[45] Murdock,[37] Allan[3] and others. A marked divergence of opinion exists concerning the nature of the mild form of secondary anemia frequently observed in pregnancy.

Among the authors who found that the erythrocyte and hemoglobin contents were unaltered throughout pregnancy, or only slightly diminished, may be mentioned Spiegelberg and Geschеildlen,[51] Wild,[54] Adachi,[1] Terhola,[52] Limbeck[33] and Engelsen.[17] More surprising is the work of Schroeder,[48] Carton[10] and Zangemeister,[56] who found an actual increase in the number of red blood cells.

That a definite anemia does exist in pregnancy was, however, shown by Fouassier,[19] in 1876, Kosina and Ekert,[30] in 1883, Meyer,[35] in 1887, Dubner,[16] in 1890, Henderson,[24] in 1902, Bar and Daunay,[6] in 1904, and Blumenthal,[9] in 1907.

Ingerslev[27] in 1879, found an average of 5.59 million red cells per c.mm. of blood in 10 nonpregnant women, and an average of 5.43 million red cells in 40 women at term. He concluded that a hydremic condition was not present, and that any difference in the counts before and during pregnancy must be due to the general health of the woman.

Thompson[53] found a high erythrocyte count at the beginning and end of pregnancy, and a low count in the interim. He noted an average hemoglobin percentage of 67.5 in the second month of pregnancy, 65 in the fourth month and 85 during the ninth month. Given[21] observed an anemia in women at term, increasing in severity shortly after labor, though the count, he claimed, would return to normal during the puerperium. Sondern[50] found a reduction of from 500,000 to 750,000 red blood cells per c.mm., and a 10 to 15 per cent drop in the hemoglobin content, during the first half of pregnancy. Dietrich[15] made blood examinations every fourteen

days over a period of three months antepartum, and found that a definite anemia was present.

Osler[41] reported a case of severe anemia in a primigravida who was well before the time of conception. The anemia was recognized in the sixth month of pregnancy. The blood examination gave 864,000 red cells per c.mm., and 20 per cent hemoglobin; also relative lymphocytosis and anisocytosis and presence of normoblasts. Spontaneous labor occurred at the end of the seventh month. The patient was reported to be perfectly well two years later.

Gram[22] records the examination of 59 pregnant women with an average of 71 per cent of hemoglobin for the first trimester, 72 per cent for the second, and 79 per cent for the third. There was also a reduction in the volumes per cent from 40 to 37. This is equivalent to a 7 to 10 per cent reduction in hemoglobin content. Adler[2] in studying 11 cases of anemia in pregnancy, found an average hemoglobin of 50 per cent and an average erythrocyte count of 3,680,000. He also observed rapid recovery to occur in the puerperium.

Larrabee[32] reported a series of 17 cases of severe anemia in pregnancy and puerperium, 8 of which were pernicious in type. He stated that the blood picture of pregnancy may be that of a secondary, pernicious, aplastic, or atypical form of anemia.

Kerwin and Collins[28] reported hemoglobin contents as low as 55 per cent. They analyzed 30 cases in the first trimester, finding an average of 83 per cent hemoglobin; 88 cases in the second trimester averaged 83 per cent, and 86 cases in the third trimester averaged 82 per cent. Balfour[5] studied 150 women with severe anemia at the Bombay Clinic in India. The anemia here occurred during the sixth and seventh months of pregnancy, in many cases associated with fever and diarrhea. Lyon[34] observed that 38 per cent of the women examined in the last trimester of pregnancy showed a hemoglobin percentage of 70 or less. Davis[14] cited 2 cases of anemia in pregnancy with a hemoglobin content below 50 per cent. Two weeks after delivery the percentage was normal. Galloway[20] found that anemia existed in all of the three trimesters of pregnancy. In the first twelve weeks of pregnancy, 87 patients gave an average hemoglobin of 72 per cent, and an average red cell count of 3.63 million. Between the twelfth and twenty-eighth week, 84 hemoglobin determinations in 77 patients rendered an average of 70 per cent, while the average of 66 erythrocyte counts was 3.56 million. Between the twenty-eighth week and term, the average of 72 hemoglobin estimations in 69 patients was 71 per cent. Forty-one erythrocyte counts, made after the seventh month, gave an average of 3.82 million.

The recent reports on the blood determinations in normal women, published by Osgood[40] and Haden,[23] have provided standards with which our results may be satisfactorily compared. Haden found an

average of 4.26 million red cells for a group of 12 normal women of all ages. Osgood reports an average of 4.8 million cells, based upon the examinations of 100 normal women between the ages of eighteen and thirty years. For the purposes of the present study the normal low limit has been set at 4 million, all patients with counts below this figure having been considered as anemic.

Results of Blood Examinations.—Table I shows that 21 (10.5 per cent) of the 200 counts in ward patients were taken in the first two trimesters, 156 (78 per cent) in the third trimester, and 23 (11.5 per cent) during labor. For simplicity of presentation, these counts have been divided into five groups. Group 1 comprises the counts of 4 million or over, and patients with this count have been considered as normal. Group 2 includes counts of 3.5 to 3.99 million cells per c.mm. (mild anemia); Group 3 comprises counts of 3 to 3.49 million cells (moderate anemia); Group 4 includes counts of 2.5 to 2.99 million cells (severe anemia); and Group 5 comprises all counts below 2.5 million (very severe anemia).

TABLE I.—RED BLOOD CELL COUNTS ARRANGED ACCORDING TO TIME OF PERFORMANCE OF TEST.

Period in pregnancy.	Number of cases.	Millions of red blood cells per c.mm.					Total number of counts below 3.5 millions.
		4.0 or over.	3.5 to 3.99.	3.0 to 3.49.	2.5 to 2.99.	2.0 to 2.49.	
Up to and including sixth month . . .	21	6	8	7	0	0	7 (33.3%)
From seventh month to onset of labor . .	156	17	52	61	21	5	87 (55.7%)
During labor . . .	23	7	10	2	4	0	6 (26.0%)
Total	200	30	70	70	25	5	100 (50.0%)

Showing that red blood cell counts below 3,500,000 per c.mm. were given by 33.3 per cent of the cases in the first two trimesters of pregnancy, 55.7 per cent in the third trimester and 26 per cent during labor.

Table I also shows that 7 or (33 per cent) of the 21 patients examined in the first two trimesters of pregnancy had a moderate anemia. Of the 156 women who were examined in the third trimester of pregnancy, 87 (55.7 per cent) had an anemia varying from a moderate to a very severe grade, while only 6 (26 per cent) of the 23 patients examined during labor had red cell counts below 3.5 million. It was also noted that 100 women, one-half of the entire group of 200 examined, gave cell counts of 3.5 million or less.

For the purpose of this study, 75 per cent hemoglobin was arbitrarily chosen as the border-line below which the patient was considered to have a low hemoglobin content. Table II indicates that

163 ward patients (81.5 per cent of the 200) had less than 75 per cent hemoglobin. It is also noted, that only 21 women had a percentage of hemoglobin higher than 80.

TABLE II.—RED BLOOD CELL COUNTS IN TWO HUNDRED WOMEN EXAMINED DURING PREGNANCY.

Hemoglobin, per cent.	Average red blood cell count.	Number of cases.	Percentage.
90 or over	4,450,000	2	1.0
85 to 89	4,320,000	1	0.5
80 to 84	4,194,000	18	9.0
75 to 79	3,774,000	16	8.0
70 to 74	3,564,000	38	19.0
65 to 69	3,440,000	36	18.0
60 to 64	3,399,000	36	18.0
55 to 59	3,174,000	14	7.0
54 or lower	2,690,000	39	19.5
Total	...	200	100.0

Showing the averages of red blood cell counts according to the estimates of hemoglobin. Note that 163 (81.5 per cent) of the pregnant women gave hemoglobin estimates of 74 per cent or less and red blood cell counts averaging 3,564,000 or less.

Microscopic examination was made of the blood spreads of every patient. In the patients in whom the count was below 2.5 million, the erythrocytes showed the distinct changes of a severe anemia. Anisocytosis, poikilocytosis and polychromatophilia were frequently observed. Nucleated red cells were not found. It may here be mentioned that the color index was below 1 in every case of anemia studied.

TABLE III.—RELATION OF PARITY TO LOW ESTIMATES OF HEMOGLOBIN DURING PREGNANCY.

Previous pregnancies.	Number of estimates of hemoglobin recorded.	Number of estimates of hemoglobin under 75.	Percentages.
None	60	47	78.3
One	37	28	75.3
Two	31	27	87.0
Three	22	20	90.9
Four	11	8	73.7
Five or more	39	33	84.6
Total	200	163	81.5

Showing that parity was not related to the low hemoglobin estimates of 163 of the 200 pregnant women studied.

The patients with less than 75 per cent hemoglobin were classified according to the number of previous pregnancies, in order to ascertain the relationship between parity and the anemia. It is observed in Table III that 60 patients were pregnant for the first time, and

that 140 patients had had one or more earlier pregnancies. Of the 60 primigravidæ 47 (78.3 per cent) gave hemoglobin estimations under 75 per cent, whereas 116 (82.8 per cent) of the multigravidæ gave a percentage of hemoglobin under 75. It is evident that parity was not related to the low percentages of hemoglobin, since over 75 per cent in each age group had a deficient hemoglobin.

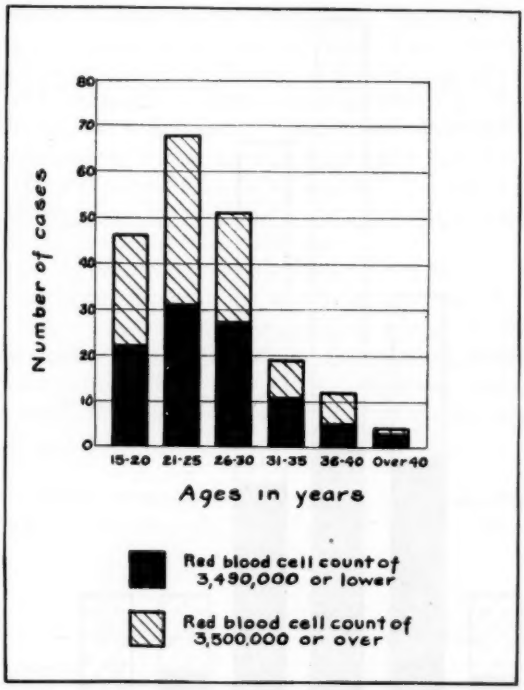

CHART I.—Red blood cell counts in 200 patients arranged according to age. Showing that approximately one-half of the women in each age group gave counts under 3.5 million cells, while the rest of them gave counts over this number.

Chart I records the number of patients according to age. It will be observed, that 165 (82.5) per cent of the patients were between fifteen and thirty years, and 35 (17.5 per cent) were over thirty years of age. Approximately one-half of the patients in each group gave counts of less than 3.5 million red cells. Inasmuch as 50 per cent of all the ward patients, regardless of age, gave red cell counts under 3.5 million, it would appear that age did not influence the incidence of moderate or severe anemia.

The systolic pressure was studied in order to disclose any possible relationship between blood pressure and the blood deficiency. The systolic pressure in 182 patients was available for study. Chart II shows that the systolic pressure in 136 patients was between 90 and

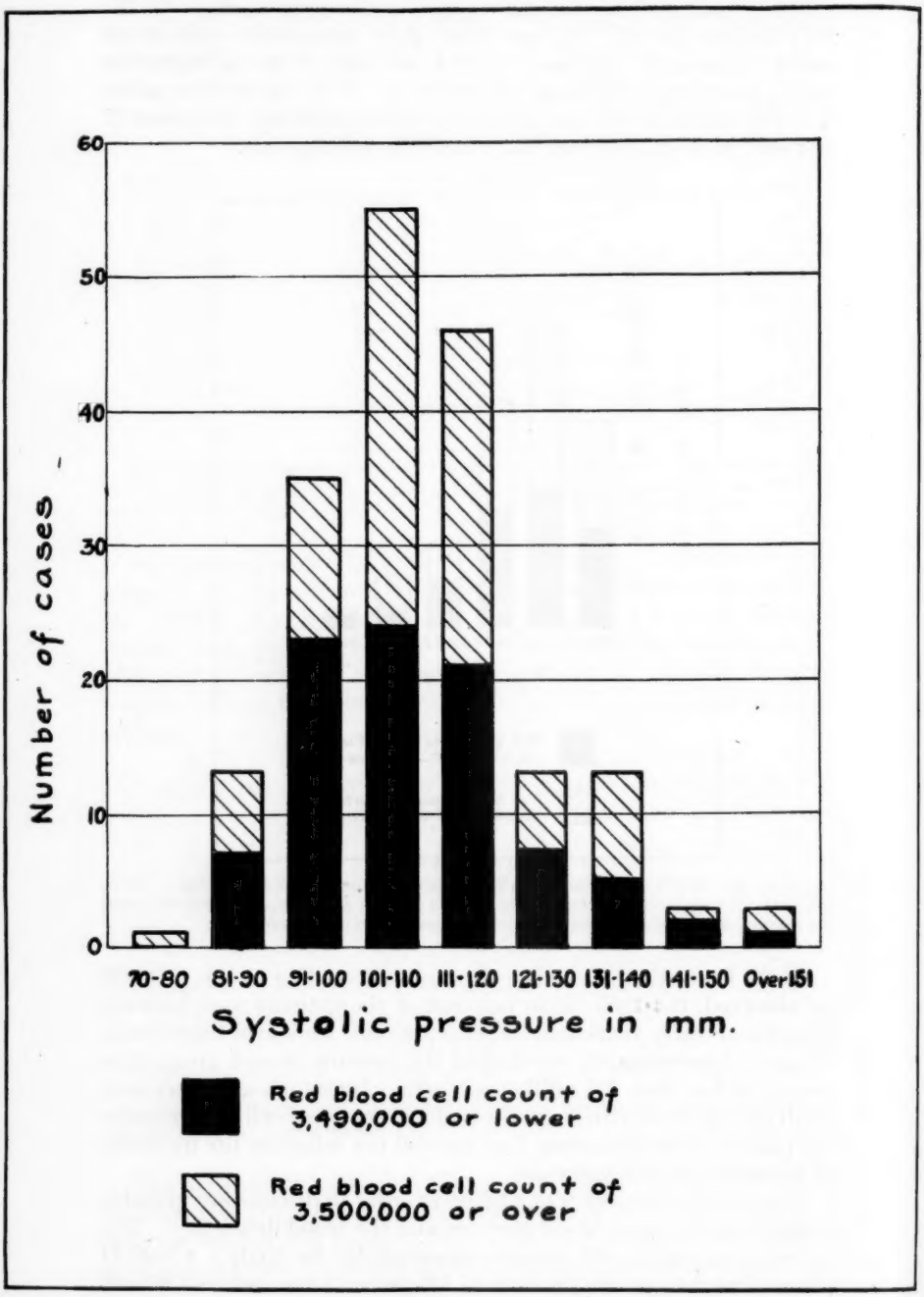

CHART II.—Red cell counts in 179 patients, arranged according to systolic blood pressure. Showing that most of the women had systolic pressures ranging between 91 and 120 mm., and that almost as many women in each blood-pressure group had counts below 3.5 million cells as had counts over 3.5 million.

120 mm. of mercury. In this group, 68 (50 per cent) had erythrocyte counts of over 3.5 million while the remaining 68 exhibited definite anemia (below 3.5 million cells). Approximately the same ratio (of counts under 3.5 million to counts over 3.5 million) existed in the groups of patients who presented a pressure below 90 mm. or above 120 mm. It is apparent that the systolic pressure did not influence the erythrocyte count during pregnancy.

Progress of the Anemia during Pregnancy. In order to determine the progress of the anemia with the advance of pregnancy, the blood counts in 35 patients made in the last month of pregnancy have been compared with the counts in these same patients prior to the eighth month. Thompson,[53] Sondern,[50] Osler[41] and Bernhard[8] found a distinct improvement in the anemia during the last two months of gestation. In a group of 42 women studied by Lyon,[34] 38 per cent showed an increase of hemoglobin in the third trimester, while 47 per cent exhibited a further diminution.

Fehling[18] noted an average reduction of 0.7 million red cells, and of 7.8 per cent hemoglobin, in the last month of pregnancy. Kuehnel[31] made erythrocyte counts every two weeks in 15 pregnant women, and found the anemia to be progressive during the first twenty-two weeks. After that, the condition would remain unchanged until the thirtieth week, at which time improvement would begin and continue after delivery.

TABLE IV.—STUDY OF THIRTY-FIVE PATIENTS SUBJECTED TO TWO RED BLOOD CELL COUNTS DURING PREGNANCY.

Number of patients.	Millions of red blood cells per c.mm. prior to eighth month of pregnancy.	Number of patients showing no change in counts at term.	Number of patients showing increase of 200,000 cells or more at term.	Number of patients showing reduction of 200,000 cells or more at term.
6	4.0 or over	0	1	5
13	3.5 to 3.90	5	3	5
12	3.0 to 3.49	1	7	4
4	2.5 to 2.99	1	3	0
35		7	14	14

Showing that increase and reduction in red blood cells at term occurred in equal number of cases. Thirteen of the women with definite anemia before the eighth month of pregnancy showed an improvement at term, while the anemia in 9 cases was more marked at term.

In our series of cases, shown in Table IV, 29 patients gave erythrocyte counts below 4 million prior to the eighth month of gestation. At term, 7 (25 per cent) of these manifested no change in the blood picture; 13 (44 per cent) showed an increase of 200,000 or more red cells per c.mm., whereas 9 (31 per cent) showed a decrease of 200,000 or more. The improvement noted in some cases is perhaps due to an attempt on the part of the bone marrow or other blood-forming organs to compensate for the apparent blood

destruction occurring in pregnancy. Diminution in the number of erythrocytes at term, is on the other hand, evidence of a more serious condition.

Course of Anemia in Puerperium. The effect of labor upon the anemia has been studied by numerous investigators. Terhola[52] found a reduction in the erythrocytes and hemoglobin immediately after labor in one-half of his cases, with no definite change in the others. He observed that the red cell count tended to increase, in most cases, in four to eleven days after labor, and that it returned to the normal level in from one to four months after delivery.

Fehling,[18] Rucker,[46] Given,[21] Meyers,[35] Dubner[16] and Sieben[49] also observed a diminution in the number of red cells shortly after labor, and attributed this loss to the hemorrhage and strain incident to labor. These authors noticed that a gradual increase in red cells and hemoglobin took place during the puerperium, and that the count at the end of two weeks was higher than during pregnancy.

Meyer[35] reported an average reduction of 750,000 red cells and of from 1 to 7.8 per cent of hemoglobin, immediately after delivery. He also attributed these changes to hemorrhage incident to labor.

Galloway,[20] in making counts on 33 patients during the first twelve days postpartum, found an average of 80 per cent of hemoglobin and 4.45 million red cells—a decided improvement over the findings during pregnancy.

The erythrocyte counts of 100 ward patients, made within forty-eight hours after delivery and again between seven and ten days after childbirth, were available for study. A comparison with the blood determinations of these same patients at term is shown in

TABLE V.—ERYTHROCYTE COUNTS IN PUERPERIUM.

Millions of red blood cells per c.mm. during last trimester.	Number of patients.	24 to 48 hours after labor.			7 to 10 days after labor.		
		Counts unchanged.	Counts reduced by over 200,000.	Counts increased by over 200,000.	Counts unchanged.	Counts reduced by over 200,000.	Counts increased by over 200,000.
4.0 or over . . . (Normal)	12	1	10 (83%)	1 (8%)	2	6 (50%)	4 (33%)
3.5 to 3.9 . . . (Slight anemia)	40	7	26 (65%)	7 (17%)	4	13 (32%)	23 (57%)
Below 3.5 . . . (Severe anemia)	48	12	8 (17%)	28 (58%)	5	9 (19%)	34 (71%)
Total . . .	100	20	44	36	11	28	61

Showing the number of patients who improved and did not improve within ten days after delivery. It will be observed that 57 of the 88 anemic patients improved in the puerperium, whereas one-half of the normal women showed lower counts during the puerperium.

Table V. It is to be noted that 12 of these patients approached term with a normal count (counts above 4 million), whereas 88 showed a definite anemia. Of the group with normal counts during pregnancy, 50 per cent manifested a definite reduction within ten days after delivery. Five of these women lost over 500,000 red cells per c.mm. The blood reduction in 2 of these 5 patients can be easily explained, as one suffered from late toxemia and was delivered by Cesarean section, while the other had developed an acute mastitis.

Of the 40 patients who exhibited a slight anemia at the end of pregnancy, 26 (65 per cent) showed a further diminution in the number of cells within two days after labor. We believe that the loss of blood incident to labor was responsible for this primary reduction in many of the patients. In 8 of the women, however, a reduction of over 500,000 red cells was noted within ten days after delivery. The complications, probably responsible for the severe loss of blood in 5 of these women were as follows: Two women had retained placentæ with hemorrhage, 1 had a premature separation of the placenta, 1 had an acute mastitis, and 1 suffered from sapremia.

Of the 48 patients with a very severe form of anemia during gestation, 28 (58 per cent) improved within twelve to forty-eight hours after delivery, and 34 (71 per cent) within ten days. A reduction of over 500,000 cells was observed ten days after delivery in 5 patients, and was believed to be caused by acute appendicitis with appendectomy in 1 case, delivery by Cesarean section at term in 2 cases, acute mastitis in 1, and sapremia in 1.

The rapid recovery, occurring in the puerperium in many of the patients with a severe grade of anemia, seems to indicate that the expulsion of the fetus would stimulate the blood-forming organs to increased function.

Erythrocyte Counts and Hemoglobin Percentages Six Months after Delivery. The blood counts of 25 patients taken six months after delivery were available for comparison with counts made in pregnancy (Table VI). Of these 25 patients, 23 had presented a definite anemia during gestation, with hemoglobin percentages varying between 45 and 76. The improvement noted was definite. One patient with a previous normal count showed a slight anemia (Patient No. 4). The anemia in 4 patients remained practically unchanged, whereas a distinct improvement—manifested by an increase of over 200,000 erythrocytes—was found in 20 cases (87) per cent). Twelve of these patients, anemic during pregnancy, had red cell counts of over 4 million on examination six months after child-birth. One patient (No. 1) showed a fall in hemoglobin, probably due to a complicating mastitis. The remarkable improvement noted in these women six months after delivery suggests that factors associated with the pregnancy itself were responsible for the anemia.

TABLE VI.—ERYTHROCYTE COUNTS AND HEMOGLOBIN ESTIMATIONS IN TWENTY-FIVE PATIENTS DURING PREGNANCY, AND SIX MONTHS AFTER DELIVERY.

Number of patients.	During pregnancy.		Six months after delivery.	
	Hemoglobin, per cent.	Millions of erythrocytes per c.mm.	Hemoglobin, per cent.	Millions of erythrocytes per c.mm.
1	72	3.72	57	3.75
2	66	3.66	64	3.60
3	76	3.80	76	4.18
4	82	4.36	70	3.80
5	85	4.40	87	4.50
6	70	3.92	83	4.40
7	74	3.70	78	4.16
8	60	3.28	100	5.07
9	66	3.20	81	3.91
10	67	3.48	80	4.16
11	70	3.88	90	4.88
12	68	3.68	76	3.88
13	72	3.65	83	4.22
14	70	3.72	78	4.00
15	43	2.36	65	3.88
16	56	3.24	68	3.78
17	76	3.93	92	4.76
18	42	2.92	82	3.70
19	74	3.26	83	4.61
20	70	3.58	84	4.31
21	65	3.54	68	3.91
22	67	3.44	72	3.27
23	71	3.42	74	3.83
24	65	3.27	70	3.86
25	45	2.56	84	4.17

Showing the results of the blood examinations in 25 patients, made during pregnancy and six months after delivery. Note that improvement occurred in 20 of the 23 patients who manifested an anemia during pregnancy. In 1 patient (Case No. 2) the presence of mastitis may have prevented recovery from the anemia.

Comparison of Blood Counts in Ward and Private Patients. The results of examinations of 100 private maternity patients have been compared with those of the ward patients, in order to determine if environment and living conditions may have any bearing on the incidence of anemia in pregnancy. Since all of the private patients were examined at term, only those ward patients who had counts taken at term were selected for this comparison. The red cell counts and hemoglobin estimations of 179 ward patients were available for study.

The percentages of ward and private patients who gave hemoglobin estimations below 75 per cent are shown in Chart III. It is observed that about 62 per cent of the private patients had a hemoglobin percentage of less than 75, as compared with over 80 per cent of the ward patients.

Chart IV shows that over 40 per cent of the private patients gave normal counts, as compared with only 14 per cent of the ward patients. The percentage of ward patients having under 3.5 million

cells at term (52 per cent) was twice as great as that of private patients (26 per cent).

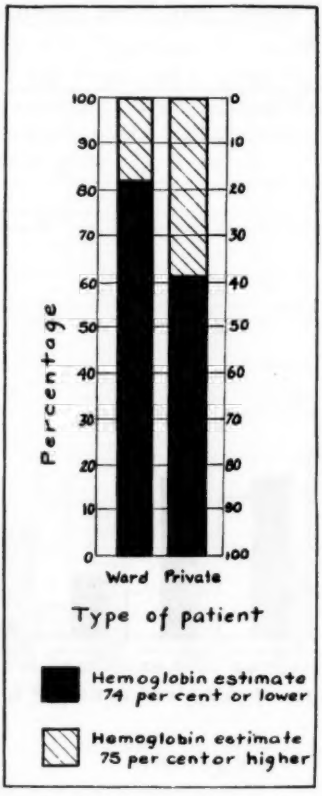

CHART III.—Percentages of private and ward-maternity patients presenting hemoglobin determinations of 74 per cent or lower, based on 200 ward and 100 private patients. Note that 82 per cent of ward patients and only 62 per cent of the private patients gave a low hemoglobin percentage.

The fact that so many private patients as well as ward patients were affected suggests that factors concerned directly with the pregnant state may have been responsible for the anemia. The influence of better environment and living conditions, however, may account for the lower percentage of private patients manifesting anemia.

Etiology of the Anemia. Several factors generally considered of importance in the causation of anemia were investigated. The importance attached to foci of infection directed our attention to the teeth, tonsils and urinary tract. Poor general health, toxemia and syphilis in the patients at the time of examination were also considered.

The result of this investigation is shown in Chart V.

Teeth were considered a source of infection in all cases in which dental caries or decay was evident. Chart V indicates that almost an equal number of women with "bad" teeth, gave counts above and below 3.5 million.

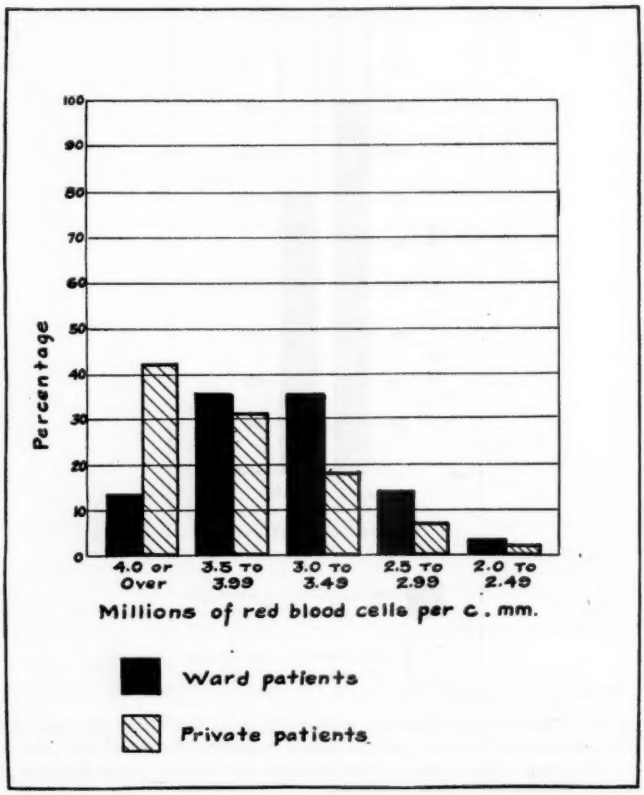

CHART IV.—Percentages of private and ward patients presenting various red cell counts, based on counts in 179 ward patients and 100 private patients at term. Note that only 14 per cent of the ward patients gave a count of 4 million or over, whereas 42 per cent of the private patients gave this count. It is observed that, for both classes, the percentages of patients having between 3.5 and 3.99 million cells are almost the same, while the percentages for ward patients having under 3.5 million cells is twice as high as for private patients.

Patients having enlarged tonsils, with a history of repeated attacks of sore throat, were considered to have infected tonsils. The study of the patients with infected tonsils brought forth results of an unexpected nature. The number of patients with supposedly infected tonsils with counts under 3.5 million was *less* than the number of these women with counts over 3.5 million.

The presence in the urine of 30 or more leukocytes per field, associated with urinary disturbances such as frequency or pain, was considered an indication of urinary-tract infection. It was realized, however, that an uncatheterized specimen did not necessarily depict the actual condition. Of 27 patients who showed over 30 leukocytes in the urine, 18 (67 per cent) had a count under 3.5 million cells. Assuming the above urinary finding to indicate infection, it would appear that involvement of the urinary tract was a contributory cause of the anemia in some of the cases.

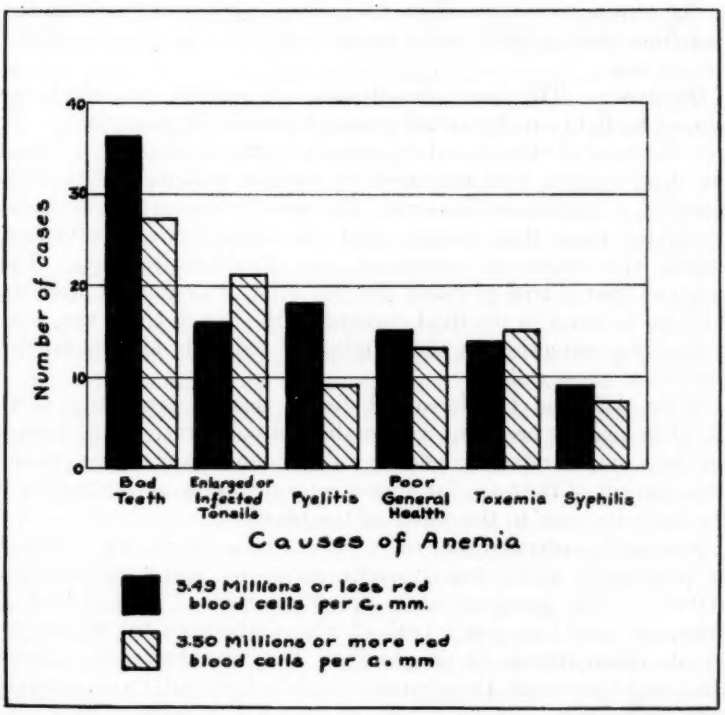

CHART V.—Classification of patients showing anemia, according to the causative factors investigated. Showing that twice as many patients with pyelitis had counts under 3.5 million as had over 3.5 million.

The general health was held to be impaired if the patient appeared to be in poor physical condition on examination, or if she complained of general weakness, insomnia, or dyspnea. The number of women in poor health who gave counts under 3.5 million was practically the same as the number who showed more than this number of cells. The state of health apparently exerted no influence on the blood condition in pregnancy.

Patients suffering from headache, exaggerated nausea and vomit-

ing, with a tendency to elevation of blood pressure (above 130 mm.), were considered as potentially toxic. Such toxemia apparently did not influence the blood picture, since the number of patients manifesting toxic symptoms was equally divided between the group showing anemia and the group not exhibiting an anemia.

A positive Wassermann reaction in a pregnant woman was taken as a criterion of syphilitic infection. Sixteen (8 per cent) of the 200 ward patients gave positive tests. The luetic patients all had erythrocyte counts under 4 million. However, the number of women with red cell counts over 3.5 million was almost as great as the number with less than 3.5 million. It cannot be admitted, therefore, that syphilis was a prominent factor in the causation of the anemia.

Discussion. The above consideration of possible etiologic factors throws no light on the actual cause of anemia in pregnancy. The specific cause of this secondary anemia remains unknown. Numerous theories have been advanced by various authors to explain the disorder. Audral and Gavarret,[4] Regnault,[43] Becquerel and Rodier[7] concluded from their studies that the reduction of erythrocytes during the course of pregnancy was of chlorotic origin. They believed that a true plethora did not exist in pregnancy, but that with an increase in the fluid content of the blood, there was a corresponding reduction in the number of red cells and in the iron content of these cells.

Willcocks[55] and Henderson[24] believed that the condition of the blood in healthy pregnant women did not constitute a true anemia, but was only a relative deficiency dependent upon the progressive enlargement of the vascular area during gestation, accounted for by the large increase in the water of the plasm.

Kiwisch[29] contended that there was a serous polyemia or hydremia in pregnancy which was brought about by increased glandular activity. The presence of a "plethora serosa" was denied by Scanzoni[47] and Cazeaux,[11] both of whom advanced the theory of a simple chloroanemia in pregnancy. They attributed to chlorosis the many functional disturbances which so frequently are associated with pregnancy.

Attention to "individual disposition" as the etiologic factor is mentioned by Peter,[42] Fehling,[18] Meyer,[35] Bernhard,[8] Schroeder,[48] Adler,[2] Dubner[16] and Reinl.[44] These authors maintained that healthy, well-nourished pregnant women have either a plethora or a normal blood condition, whereas the weak and undernourished women manifest a chlorosis. Ingerslev[27] also adheres to this belief, although he found counts of 5 million in the healthy as well as in the undernourished woman. Kuehnel[31] likewise reported the presence of anemia in the apparently full-blooded, as well as in the less robust individual.

Hofbauer[25,26] believed that a syncytial hemolysin in the ectoder-

mal cells of the chorion was the cause of the maternal blood destruction in early pregnancy, and the increased iron content in the urine of pregnant women somewhat favors this theory of blood destruction. He contended that the physiologic anemia was overcome in the second half of pregnancy by an antihemolysin formed in the maternal blood but that if this function failed, an active hemolysis and progressive anemia would continue during pregnancy and after delivery.

Adler[2] held that the so-called pernicious anemia of pregnancy occurred only on the basis of a primarily injured bone marrow. Sondern[50] found anemic gravid women in whom the usual causes of anemia, such as poor hygiene, nephritis, syphilis and tuberculosis, were not present. Lyon maintained that the anemia of pregnancy represented a preëxisting anemia which had continued in pregnancy, since he observed a similar anemia in a group of nonpregnant women with retroversion of the uterus.

Certain facts brought forth by this study have convinced the authors that factors, as yet unknown, connected with the gravid state are, directly or indirectly, responsible for the anemic condition so frequently observed in pregnant women. The fact that the private patient coming from an environment conducive to good health manifested an anemia, although not as severe as the ward patient coming from unfavorable surroundings, indicates that the pregnancy *per se* in some manner had produced the blood deficiency.

The assertion that only a relative anemia exists in pregnancy is a disputed matter. It is generally recognized, that the vascular area is considerably and progressively enlarged in pregnancy because of the increase in the water content of the plasm. If one assumes that the number of erythrocytes is not diminished in pregnancy, then the dilution of the blood which occurs as a result of the increased enlargement of the vascular system would manifest itself in a lowered cell count. A relative anemia would then be the natural result.

The spontaneous recovery, ensuing in most cases within ten days to six months after delivery, points to a return of the maternal circulation to the volume of the nonpregnant state. The improvement also indicates that the anemia did not exist prior to the onset of pregnancy. It is conceivable, however, that some of the patients who became more anemic within ten days after delivery may have been deficient in blood before the beginning of gestation. Complications of labor or of puerperium, associated with hemorrhage or sepsis, were uncovered in several of our patients who did not improve after labor. Thorough examination of recently delivered women, in whom the anemia persists, may disclose causative factors similar in nature to the ones found in several of our patients.

Patients with hemoglobin determinations below 75 per cent and red cell counts under 3.5 million should be particularly observed, and therapeutic measures instituted immediately upon discovery of

deficiency. These patients should be watched for several months after delivery, and microscopic blood studies made in order to secure evidence of beginning bone-marrow changes.

Summary and Conclusions. The following facts and observations were brought out by this investigation:

1. Of 200 ward maternity patients, one-half exhibited a definite anemia during pregnancy, with red cell counts below 3.5 million per c.mm. Of 100 private patients at term, 26 per cent gave counts below 3.5 million. It was found that 126 (42 per cent) of the entire group of 300 gravid women studied, regardless of the time of examination, gave counts below 3.5 million cells.

2. It was found that 82 per cent of the 200 ward cases, and 62 of the 100 private maternity patients, gave determinations of hemoglobin of 74 per cent or less.

3. The severity of the anemia is apparently not affected by parity, age, or blood pressure.

4. No conclusive evidence was discovered to confirm or disprove the contention of other authors that improvement occurs at term. In a study of 35 patients, having two blood determinations in pregnancy, we found in 14 a gain of 200,000 cells or more and a reduction of the same number of cells in 14 others.

5. Several etiologic factors, including ill-health, foci of infection, toxemia and syphilis, were investigated, but the extent of their influence was not sufficient to be determined.

6. The most interesting fact disclosed by this study was the remarkable and rapid recovery occurring in a large number of women within a few days after delivery. It was found that 34 of 48 women (71 per cent), having red cell counts below 3.5 million in the last trimester of pregnancy, gained over 200,000 cells per c.mm. within ten days after delivery. Of 23 patients, definitely anemic during pregnancy, 20 were observed to have practically fully recovered in six months after delivery.

7. The large percentage of private patients with anemia indicates that environmental circumstances alone were not responsible for the anemia.

8. The etiology of the anemia of pregnancy remains undisclosed. The withdrawal of iron from the maternal corpuscles by the fetus, the existing hydremia of pregnancy, and a preëxisting chlorosis, all these are probable factors in its production. Further investigation is required to throw light on the fundamental nature of the secondary or so-called physiologic anemia of pregnancy.

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ANEMIA OF THE NEWBORN.

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In the last few years several authors have written of a rare form of anemia, the anemia of the newborn. Six cases have been reported one each by Ecklin,[1] Donally,[2] Susstrunk,[3] Sanford,[4] Bonar[5] and McClelland.[6] The case to be described conforms to the others in most respects, with certain exceptions to be noted later. Though

only recognized recently, it is probably a rare condition. Even those infants which are soon to become anemic, have, as Lichtenstein[7] has shown a normal blood picture at birth.

Case Report. *History.* N. H., a girl, white, was born March 20, 1929. This was the first pregnancy. Labor was induced a few days before the expected time of confinement because the mother had hypertension, albuminuria and some toxemia. A chronic cholecystitis had been diagnosed during pregnancy. The mother's blood count on the day of delivery was as follows: Leukocytes, 12,000; erythrocytes, 3,930,000; hemoglobin, 74 per cent; polymorphonuclear neutrophils, 79 per cent; lymphocytes, 21 per cent. The delivery was instrumental, high forceps being used. The birth weight was 5 pounds 9½ ounces. The infant was first seen on March 21, when two days old.

Examination. The infant was small, pale and listless, with a shrill cry. The anterior fontanelle was quite tense and slightly bulging. There was no jaundice. The skin and mucous membranes were strikingly pale. The pupils were equal and reacted to light. The heart and lungs were normal. The abdomen was not distended and neither liver nor spleen could be palpated. The lower extremities were rigid and the reflexes hyperactive. A lumbar puncture revealed a blood-tinged fluid and 5 cc. was removed. The fontanelle was then found to be less tense and somewhat depressed. A blood examination at this time (March 21) was as follows: erythocytes, 1,780,000; hemoglobin, 48 per cent; color index, 1.3−; leukocytes, 17,000; polymorphonuclear neutrophils, 76 per cent; lymphocytes, 18 per cent; mononuclears, 5 per cent; eosinophils, 1 per cent; blood platelets, 260,000. There were a few nucleated red cells and moderate anisocytosis. The patient and father were both in Group 1.

On the third day after birth (March 22) 100 cc. of whole blood from the father was given to the patient. There was no reaction and no rise in temperature. On March 23, the day after transfusion, the blood count was as follows: erythocytes, 4,150,000; hemoglobin, 80 per cent; color index, 1−, leukocytes, 9400; platelets, 320,000; polymorphonuclear neutrophils, 74 per cent; lymphocytes, 25 per cent; eosinophils, 1 per cent. The patient was much brighter, the color was good. There was no evidence of cerebral irritation and the fontanelle was soft. Feedings were taken fairly well. Three days after transfusion the erythrocytes were 5,370,000 and the hemoglobin was 90 per cent. At no time was the spleen felt. The infant appeared normal in every respect. At the age of four months the blood was examined again and the erythrocytes were 4,500,000 and the hemoglobin 80 per cent. The weight was eleven pounds. The color was good and the infant was bright and active. The spleen could not be palpated.

Comment.—The etiology of anemia of the newborn is obscure. A possible cause in this case (hypertension, albuminuria and toxemia in the mother) cannot be ignored, although the mother was not particularly anemic. Bland and Goldstein[8] have recently shown that 50 per cent of pregnant women have erythrocyte counts below 3.5 million per c.mm. This anemia is only temporary as 92 per cent of 50 patients showing anemia in pregnancy made a spontaneous recovery within six months after delivery. Toxemias of pregnancy in the mother do not usually cause severe anemia in the

newborn, and the rarity of such anemias would indicate that there is some other factor responsible. This is the only case reported where the mother had hypertension and toxemia. There is also the possibility that the anemia was due to intracranial hemorrhage. The spinal fluid was blood-stained and the fontanelle tense. However, after one lumbar puncture the infant's condition was so much improved that no further treatment was necessary. The hemorrhage, therefore, could not have been large. It is interesting to note that in the case reported by Donally, there were signs of cerebral hemorrhage. A slight cerebral hemorrhage in the newborn does not cause as severe an anemia as was present in my patient. The other causes of anemia in the newborn can be ruled out. At no time was there bleeding from the mucous membranes, purpuric spots, or jaundice. There was no evidence of tuberculosis or syphilis. There was no fever at any time or signs of sepsis.

Summary.—It would seem that anemia of the newborn is a definite clinical entity, as evidenced by the similar blood picture in all the reported cases, the good prognosis and the permanent improvement after the infant reaches the second half of the first year. The true etiology is probably to be found in some temporary defect in the blood-forming tissue of the infant, but this is only conjecture. The recovery of infants with this type of anemia is usually complete in a few months. In the cases described by Ecklin, Sanford and Bonar, recovery was effected without blood transfusion. This proves that there is no permanent injury of the blood-forming organs. Only one case has proved fatal (Susstrunk) and here autopsy failed to reveal the cause of the disease. Anemia of the newborn is similar to hemorrhagic disease of the newborn in that the blood defect in each disease is temporary and recovery may occur without treatment. Blood transfusion in anemia of the newborn is the treatment of choice and in my patient produced an immediate cure.

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THE ECZEMA PROBLEM.*

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Not all dermatology concerns itself with polysyllabic rarities of small moment to medicine as a whole, or with the minor surgery of cosmetic blemishes. Within the field lie some of the crippling ills of mankind. Eczema, in certain senses of the term, is one of these, and to its study at this moment a generous share of energy and brain power is being devoted. It evidently occurred to your secretary, as to me, that you would be interested in a statement of our present position in regard to this problem.

First let me attempt a redefinition of the term eczema in line with current conceptions of the trend of dermatology away from the purely descriptive toward the more fundamentally etiologic viewpoint. Eczema is a dermatitis, a catarrhal cutaneous inflammation in which exudation or secretion of fluid is a conspicuous feature. Does this quality justify the separation of eczema from the multitude of other forms of dermatitis? I believe not. Inflammation, with its fundamental pathologic reaction signs, is simply a form of sign language, a cry of protest, aroused by etiologic stimuli, and in the end classifiable best on the basis of the stimuli, rather than, figuratively speaking, on the minor tonal and pitch variations of the cry. Before defining eczema, then, let us attempt an etiologic definition of dermatitis, for the causes of dermatitis embrace those of eczema. A dermatitis is a cutaneous inflammation aroused by the interaction of two groups of causes, constituting a foreground and a background of the picture; predisposing causes, largely in the constitutional background, and exciting causes, the immediate usually irritant accidents or contacts. The exciting cause, if I may quote myself and change the metaphor, acts as the trigger pull to the already existing load of predisposing causes, and the result of that interaction is a cutaneous explosion in some one or other of the many inflammatory forms, ranging from hives to eczema.

It follows, then, that a thoroughgoing and sometimes highly complicated analysis must precede the therapeutic decision in each individual case of dermatitis, if lasting good results are to be secured, in the effort to unravel the interaction of predisposing and exciting causes and to apply the proper treatment to each. In order to assist my students in this process, I have prepared an analysis of present knowledge on this subject, given in the body of this text. In a sense this analysis constitutes a species of desk card, against

* Read before the West Virginia State Medical Association, Martinsburg, W. Va., May 22, 1929.

which the case before one can be analyzed as the patient is questioned and studied.

THE CAUSES OF DERMATITIS.

I. *Two Groups.* *Predisposing causes,* which form the constitutional background, on which dermatitis develops, and *exciting causes,* the immediate, usually irritant accidents which precipitate the cutaneous explosion, acting as a "trigger to the charge of predisposing causes."

II. *The Predisposing Causes.*

1. *Race.* Blonds predisposed. Neurotic racial strains.
2. *Age.*
   (*a*) *Infancy and Childhood.* Predisposed to the allergic eczemas, the superficial pyogens, the exanthems, the scalp ringworms, animal parasites.
   (*b*) *Prepuberal and Puberal Years.* In addition to the above, the seborrheas, psoriasis.
   (*c*) *Young Adult Life.* The epidermophyton ringworms of feet, groins, hands, seborrheic dermatitis, lymphomatosis.
   (*d*) *After Thirty-five Years.* The occupational dermatitides, eczematoid dermatitis, seborrheic dermatitis, cutaneous neuroses, lymphomatoses.
   (*e*) *After Fifty Years.* Involution dermatitis, a complex of decreased elimination, accumulating infections, nervous overload and so forth.
3. *Infection.*
   Focal. Teeth, tonsils, sinuses, appendix, bronchiectatic conditions, gall bladder, colon, prostate, cervix.
   Systemic Associations. Intestinal parasitism (ascaris) and dermatitis, variola and pyogenic infection, streptococcal and staphylococcal septicemia and the purpuras, toxic erythemas and erythema multiforme group.
   Local. Abscesses, draining sinuses, suppurations, etc.
4. *Parasites.* Pediculosis, scabies, postscabetic sensitization. More rarely, mosquitoes, bedbugs, straw mattress mites, fleas, chiggers.
5. *Neoplasms.* Lymphomas, leukemias. Various neoplasms, through invasion of the liver or obstruction of the biliary tract, with the production of jaundice.
6. *Abnormalities in Blood Chemistry.* While much studied and theorized about, abnormalities in blood chemistry are few in dermatitis and of doubtful etiologic significance. This includes sugar, chlorids, uric acid, nonprotein nitrogen and calcium. Photosensitive substances; hematoporphyrin the only known example.
7. *Disturbances of Diet.* High carbohydrates especially; rest and exercise.
8. *Disturbances of Intake-output Ratio.* Metabolic effects of overeating, underexercise and waste retention (nephritis, constipation).
9. *Gastrointestinal Disturbance as Such.* Hypochlorhydria and achlorhydria, colitis, colonic and intestinal stasis, spasm and spastic disturbances.
10. *Excessive Sexual Activity and the Puberal State.* Pyogenic and seborrheic lesions.

11. *General Sensitivity.* Indefinable by our present knowledge. Due to proteins? Histamines? Bacterial decomposition products? Intestinal disturbances? Vagotonia? Vasomotor instabilities? Pluriglandular syndromes?
12. *Nervous Overload and Disturbance.* Including sexual complexes, inferiority complexes, anxiety neuroses, and so forth. Acts through:
    (*a*) Endocrins (thyroid and adrenals).
    (*b*) Vasomotor mechanism (rosacea, urticaria).
    (*c*) Sympathetic-vagus system (urticarias, rosacea, neurogenous dermatitis). Includes action on digestive secretions, intestinal peristalsis, etc.
    (*d*) The sensory mechanism of itching (unknown).
13. *Endocrin Abnormality as Such.* Low basal-metabolic rate. Hypothyroidism. Menstrual disorders, especially amenorrhea.
14. *Cutaneous Dystrophies and Functional Abnormalities.*
    (*a*) *The Ichthyotic State.* Dry skin, slightly scaling forehead and scalp, pretibial region, follicular plugging of the extensors, parchment palms.
    (*b*) *Seborrhea.* Hyperactivity of the sebaceous glands. An endocrin background (?).
    (*c*) *Hyperidrosis.* Perspiring palms, soles, scrotum, axillæ. A "sympathetic" neurosis (?).
    (*d*) *Vascular stasis.*
        1. Vasomotor (rosacea, blue hands and feet and so forth).
        2. Mechanical (varicose and thrombotic).

III. *Exciting Causes.*

1. *External Irritants.*
   Occupational contacts.
   Drugs and medicaments.
   Chemicals.
   Cosmetics.
   Vegetable poisons (Rhus, and so forth).
   Light, heat and cold. Mechanical agents (friction).
2. *Allergy-producing or Exciting Agents.*
   (*a*) *Specific.* Food and other proteins, pollens, plants, animal products (hair, fur and so forth).
   (*b*) *General.* Serums, bacterial toxins, vaccines.
3. *Infections.*
   (*a*) Ringworms (dermatophytids, in which the organism is not present).
   (*b*) Streptococcus and staphylococcus infections, local and general.
4. *Parasites.*
5. *Trauma.*
6. *Nervous shock.*

If then, etiologically speaking, this be dermatitis, what is eczema? Over this question, which brings to a focus all the problems of direct and indirect etiology, the battle still rages. A powerful and extremely modern group, with whom, it must be conceded, rest many of the laurels of distinctive scientific achievement, insists that extrinsic or exciting cause and not constitutional background is the etiologic force and fact in eczema as it is in dermatitis. There is, therefore, according to this group, no difference between eczema

and dermatitis, etiologically or pathologically. A second group, for whom Pulay has been a recent spokesman, insists that eczema is fundamentally a constitutional disease and that, whatever the exciting cause that may be unearthed, it reacts upon an essential and indispensable susceptible background. Moreover (and here is the crux of the issue), an eczema persists and may extend, it is contended, even after the removal of the determined exciting cause—the best evidence of the potency of the constitutional element.

After all, it seems to me both groups are in a sense right, and that the apparent disagreement is more a matter of relative emphasis than of fact. A compromise position can be stated which allows both sides their due. I, therefore, for the purposes of discussion, define eczema to you as:

"A form of dermatitis in which the constitutional background has come to outweigh the exciting cause, though both are present at the outset, and may continue present throughout the picture."

On the other hand, as Pulay puts it, irreversible changes may occur in the skin, or it may be so predisposed by the patient's inherited constitution that the dermatitic process is perpetuated as eczema, even after the withdrawal of the extrinsic exciting cause.

Crudely speaking, one may illustrate this difference by example. A given person in ordinarily good general health may sit down in, or handle poison ivy, and develop the typical picture of a dermatitis venenata, which subsides under ordinary soothing treatment in ten days. A second person with a background of predisposing causes develops poison ivy under the same conditions and at the same time, and in his case the process not only does not subside in ten weeks, instead of ten days, but it spreads to other parts of his body, which have had no contact with the irritant oil as such. Months after the removal of the exciting cause he is still suffering from extensive patches of eczema which respond, if at all, only to measures that fundamentally change not only the physicochemical background of his skin but the autonomic-sympathetic balance of his nervous system, the cellular reactions of his body tissues, the behavior of his hematopoietic system, the reactions of his gastrointestinal tract and even his whole outlook on life. In the process of readjusting this fundamental constitutional background, everything may have failed until with the extraction of an infected tooth, the drainage of an antrum, the removal of an infected gall bladder or the reëducation of the patient with respect to a mother-in-law, the whole process has begun to mend, and has stayed mended so long as the individual remains in balance with his predisposing background. He may remain susceptible to poison ivy, but an attack will clear up comparatively rapidly until his constitutional ledger again shows a debit. Then he will have another siege of "eczema," to be dealt with in the same way.

I am sure it will be apparent to you, then, that the study of

the etiology of eczema will carry us far afield, into a variety of medical problems, among the foremost of which will be those of allergy or hypersensitivity, in which so many important advances have been scored in the last few years by Jadassohn, Coca, Zinsser, Doerr, Bloch and their students and co-workers. There is a tremendously convincing quality about a demonstration such as the Prausnitz-Kustner or the Walzer technique of predicating the presence of an antigen in the blood serum of the susceptible individual, responsible for an interaction between the offending external substance or cause, and the patient's tissues; an antigen which has the highest degree of specificity for the incriminated substance. Such demonstrations rightly give the claim of the "externalists," who insist that every dermatitis and eczema has an extrinsic cause, a remarkable degree of force and convincing quality. Under the influence of this school of thought innumerable substances, toxins, organisms and contacts have been found to produce dermatitis and to underlie what had previously been regarded as eczema of exclusively internal or intrinsic causation. Today, the list of exciting causes which the conscientious and well-equipped dermatologist must be prepared to hunt down in any given case ranges from the ink of the Sunday rotogravure supplement and the celluloid rim of the eyeglass to the hair of the son's pet guinea pig, the fungus between the patient's fourth and fifth toes, the plant on his dining-room table, the seasoning in his soup or the roundworm in his gut. One look at a rubber shoe heel containing hexamethylene as a catalyzer will send the workmen of a factory into frenzies of dermatitic protest. Steam-distilled is alleged to differ from old-fashioned turpentine. Though a man may not, by Holy Writ, live by bread alone, it appears that he may have eczema by it alone and fill the columns of the German literature with dissertations on bakers' dermatitis. Though I seem to use a facetious tone, I say in all sincerity, more power to the discoverers of exciting causes. They have at least convinced us of the eminent worthwhileness of determined search of the visible and contact world for the explanation of a dermatitis or an eczema. Such a search should always be made before we proceed to appraise the internal, the invisible and the as yet to some extent speculative elements which go to make up the constitutional background suggested as the line of differentiation between dermatitis and eczema. On pain of being declared lazy then, let us not neglect the thorough search of our patient with eczema for the external causes of the dermatitis which afflicts him.

But shall we stop there? Is there not something suspicious about this amazing accumulation of external irritants which will set someone somewhere into cutaneous spasms? Is it in keeping with our general knowledge of the plastic interaction that occurs between parasite and host, between donor and recipient, between this human

protoplasmic gel and the agents that creep and crawl across it or push and prod against it, that there should be no internal predisposing reactive mechanism to be studied in connection with the effect of an irritant coming from without? Is it not conceivable that study of the reactor may disclose a nonspecific as well as this startlingly specific mechanism of reaction which has so usurped our recent attention? To this point of view the eminent British student of occupational dermatoses, Prosser White, I think it was, led the way in linking to the local effects of industrial irritants, a systemic predisposing background, including therein the effects of age and worry and of the seborrheic makeup, grounded as it is in the carbohydrate metabolism. To these more obvious elements the school of Kreibich and such observers on the neuropsychiatric borderline as Sack are adding a neurogenous background. The studies of Klauder on the calcium-potassium balance in its effect on the vagus-sympathetic system, while still on chemically unstable ground, are giving some elements of tangibility to the hypotheses centered around that *terra incognita* of the human being, his vegetative nervous system. Bloch is undoubtedly right in asserting that the tangibilities are on the side of the externalists and that they are advancing much faster for the moment in their share of the working out of the etiologic mechanism of dermatitis and eczema. The students of intrinsic causes, the scientific as distinguished from the intuitional side of whose work is so fraught with pitfalls of subjectivity and experimental difficulties, are still far in the rear. But there is no justification for a refusal of either side to recognize the existence of the other, or for the specifists to deny the influence of a general predisposing mechanism among the causes, merely because mental stress, for example, is not as visible and measurable as the dose of primrose extract which will induce sensitivity in a normal and previously unsusceptible subject.

What then is the eczema problem of today? It consists in an effort to unravel the details and to make a statement of the laws governing the specific reactivity of an individual to the exciting cause coming from without which is giving him or has given him an eczema; and an equally clear definition of the type and methods of action of the *internal* disorders and disturbances of function and structure which contribute to and perpetuate his abnormal reactivity to stimuli, specific or nonspecific.

Turning then once again to the schedule of causes of dermatitis, one finds therein many evidences of the sifting-out process with respect to the older conceptions of eczema, that today confuses the practitioner whose dermatology dates back twenty or even ten years. Many things that passed as eczema in the texts and teachings of only a decade ago are now being recovered from the catch-basket and pigeonholed as well-defined entities. This is particularly true of dermatitic reactions due to infections. The best

examples lie in the field of the mycotic or fungous lesions of the skin. Many of the former "chronic eczemas" of the hands and feet are now recognized either as actually due to a fungus, usually some member of the epidermophyton group of fungi or as secondary sensitization phenomena, spoken of as dermatophytids. The eczemas of the axillæ, groins and anogenital region, known for years as intertrigoes or flexural eczemas, are falling into the same group. Castellani among others has given much attention to these types. The moist and freely-perspiring regions of the body, and particularly those whose sweat and circulatory mechanism is markedly influenced by states of nervous stress or excitement, are ideal sites for the development of mycotic eczemas. In some of their forms, as particularly in the so-called eczematoid parakeratosis, which affects the submammary and inguinal regions of elderly women, with frequent coincident involvement of the skin behind the ears and in the umbilical depression, the instrumentality of a fungus or of some infectious agent seems almost undoubted. The clinical picture is as distinct an entity as herpes zoster. Culture, however, may fail to identify anything but a mixture of pyogenic organisms, often unusual types of streptococci, possibly because of unsuitable media or growth conditions.

Evidently, then, the bacterial and mycotic flora of eczema is a problem of the first order; to be studied, let me insist again, from the standpoint of the favoring conditions in the patient which promote such growth and such distinctive localization, quite as much as the classification and type of the organism. In the one direction, as evidence of the trend of the time, we find the observations of MacLeod and his co-workers in England, and of Cleveland White and C. J. White and others in this country, tending to indicate that what have been called seborrheic eczemas are yeast infections on a susceptible background. The observations of Fordyce, Sutton, and recently of Herbert Mitchell, on the other hand, point toward pyogenic organisms as responsible for other distinct types of what used to be eczema, particularly of the extremities. The newer terminology, then, should recognize a concept within the old "eczema" category. This is "eczematoid dermatitis," of mycotic (yeast) or infectious (pyogenic) origin. The former group includes attendant allergic phenomena in specially susceptible individuals and the latter includes eczemas apparently traceable to pyogenic organisms, yet without the distinctive pustulation, crust and bulla formation of the impetigoes. The whole problem is complicated by the question of contaminants and saprophytes as against pathogenic organisms. A number of years will probably be required to establish conclusively the causative as distinguished from the merely coincidental or contributory rôle of some of the microörganisms now put forward as responsible for various forms of dermatitis and eczema. Be that as it may, the group of infectious eczematoid

dermatitides is the most recent branch from the ancient parent trunk of eczema. The importance of the factor of individual constitutional background even in this new group is well illustrated by the fact that certain of the investigators mentioned have been successful in their attempts to carry through the postulates of Koch, only by inoculation upon the skins of the patients who were already victims of the "eczema" they were investigating. Normal skins, as noted by both MacLeod and White, do not give typical lesions on inoculation of cultures. Even here, then, the constitutional background outweighs the external exciting cause.

In the background of eczematoid dermatitis, as I have seen it, lie the elements of a disordered cutaneous carbohydrate metabolism or an excessive carbohydrate intake; the congenital anomaly of the fat secretion mechanism and the keratization cycle known as ichthyosis; gastrointestinal dysfunction, especially hypochlorhydria; elements of nervous stress, fatigue, overwork and strain; focal infections in tonsils, teeth, sinuses, colon, gall bladder or perhaps prostate; allergic elements, including susceptibility to special irritants and the atopy to be presently mentioned as occurring in true diathetic eczemas.

With intertriginous eczema, seborrheic eczema and infectious eczematoid dermatitis being gradually reinterpreted with respect to their balance of constitutional and external exciting causes by an increasing clarification of the local factors, there remain to be accounted for under the general concept of eczema, the so-called nurslings' eczema of the German writers; metabolic eczema; involution eczema and, finally, neurogenous eczema and the so-called diathetic or constitutional eczema which forms the third member of the eczema-asthma-hay-fever complex. In these groups the constitutional background still appears to maintain the upper hand in the etiology.

The term infantile eczema, as commonly used in this country, covers a variety of types. The seborrheic or carbohydrate metabolism factor is chiefly responsible for one group, which responds to a reduction in starch and sugar intake and a substitution of fats. Essentially this is seborrheic eczema in the child, then, from the constitutional standpoint. Another group of infantile eczema cases undoubtedly can be classified as infectious eczematoid dermatitis—the pustular pictures which are not impetiginous, the extensive, even universal eczemas of infancy with marked lymph-node involvement and occasional abscess formation or alternating bouts of multiple furunculosis and eczema. A third group includes the allergic eczemas, in which cutaneous tests demonstrate a reactivity to certain food proteins, notably those of milk, beef, eggs and wheat, and from which recovery takes place on withdrawal of the incriminated substance. This last-mentioned is perhaps the true nurslings' eczema of the German writers. The term infantile eczema,

as used in this country, includes all of them and success in their management is to some extent dependent on ability to identify the most influential factor by a careful local and general examination and a detailed dietary and habit history. Close on the borderline of infantile eczema lies that most interesting complex of dermatology in children, a curious mixture of eczema, urticaria and erythema multiforme, called lichen urticatus, in which neurogenous factors mingle with local, dietetic, infection and sensitization elements in a most intriguing interplay. Included in what is commonly called infantile eczema is, too, a proportion of cases which represent the early symptomatic appearance of the true diathetic eczema to be presently described.

Metabolic eczema is a concept of decidedly hazy definition, and one more often, I think, misused than correctly applied. A typical example would be the type of eczematous and dermatitic change which is seen most often in young girls in association with subnormal basal metabolic rates indicative of endocrin deficiencies. The response of some of these patients to thyroid medication is undoubted. But as one observes a succession of them, one wonders whether it is the thyroid as such that brings about the improvement, if any occurs, or whether it is not simply the action of the drug as a vasodilator, with the consequent stimulation of the keratization cycle of the skin, and the raising of its general nutrition through a freer blood supply, rather than a distinctive endocrin action as such. Undoubted cases of ichthyosis in young persons, for example, can be transiently improved by the administration of thyroid, which makes them sweat—but if the drug be continued they quickly show signs of hyperthyroidism, as would a normal person, and if it be dropped they recur to the original cutaneous condition. The action would in such cases seem to be incidental and symptomatic rather than fundamental. That there is a metabolic element in many eczemas seems probable, but that it is causative of the cutaneous picture, and not merely another symptom of some underlying disturbance, probably of the sympathetic nervous system, is the impression one gets from repeatedly working up such cases. The significance of the basal rate of -4 to -14 in these patients, so often stressed by internists venturing into dermatology, together with the disturbance of gastric secretion in the direction usually of hypoacidity; the low blood pressure; the irregular menstruation, alternately retarded and overfrequent for considerable periods; the vasomotor instabilities; the occasional suggestion of acromegaly—all these things point toward endocrin disturbance. Their intimate significance, however, so far as thyroid, pituitary and other endocrin glands are concerned, is as yet far from explanation. There are undoubtedly metabolic factors in eczema, but their meaning is still obscure.

Involution eczema includes the intractable dermatitides of later

life, which so much too often torment what should be a peaceful old age. Here, too, is a field full of problems, and no entity is precisely definable. The ears, scalp, groins and extremities are most often involved. A search for every available external irritant explanation in these cases often leaves one with nothing tangible. The patient is simply old and worn out. Focal infections may be identified, but there is no result from their removal, the trouble being simply transferred to some other point in the patient's weakened economy. Time and again it has seemed to me, for example, that the chronic bronchitis superposed on emphysema in the aged in this climate, is an important element in the irritable senile skin. Physiologic decline of the fat-secreting power of the sebaceous glands leaves the skin relatively more susceptible to bacteria and external irritants. Winter drying and artificial heat, toothless mouths that cannot chew food, senile achlorhydria, the train of prostatic difficulties, the chronic joint focus, the ancient and honorable "gouty diathesis," all mingle in a depressing background of decay. One is tempted again and again to write a thesis upon *worry* as the background for the itching skin and scratcher's dermatitis of old age. Yet it is imperative to resist the temptation to fall back on generalities until every individual item of local importance has been accounted for. How often have I been inclined to accept involution eczema as a diagnosis, ultimately to find that bandage support of a mild grade of varicose veins did away with the persistent tendency to eczematous outbreaks on the senile leg. How often have I laughed as a patient told me of his "gouty diathesis" diagnosis, when less soap and more grease, or an attack on the ringworm between his toes, gave him relief. But years of observation have only strengthened my appreciation of the importance as an index of constitutional overload, of the appearance of an eczema after the age of forty-five.

Every medico has his hobby; mine, I frankly confess, is the neurogenous factor in dermatoses, so that in presenting it to you, you will smilingly indulge a little enthusiasm on my part. Yet it *is* interesting to see how the horizon is widening in this direction among dermatologists. A state of mind, acting through the vasomotor system, and the as yet unknown mechanism of itching, *can* underlie the appearance of a dermatitis and nothing will finally avail to control it until the mind is set at rest. It is true, that there is usually an exciting cause identifiable, but it is so far nonspecific that at one time it may appear to be one thing, and at another, a different thing. A woman, worried with good cause about her husband's health, develops a dermatitis of the neck, of that type so familiar to me as a feature of my eastern transplantation that I call it "Philadelphia neck." Ingenious devices to protect the neck from irritants fail, and a full schedule of sensitization tests reveals that squirrel fur is the alleged exciting cause. The squirrel

coat is put away; the neck clears up. Two months later, when the worry has again become acute, the trouble reappears, this time without the intermediation of squirrel. The same picture develops time and again in women quarrelling with daughters who stay out too late; in women traveling wildly to escape the boredom of an old age with duties but no interests; in women, the ambitious wives of unambitious, retiring and scholarly husbands; in women with flower gardens but also with husbands forty years too old; in women who recover and yet keep their gardens, when their philosophy of life has triumphed over the seeming *impasse*. Just as Bloch has shown that it is possible to remove warts by psychotherapy and nothing else, so it may some day be shown by some sufficiently bold explorer, that it is possible to remove some forms of eczema by the same means. Today, however, I only claim that the mind and the nervous system provide the source and the transmitting mechanism for a powerful group of predisposing causes in the etiology of eczema.

Just how the nervous system acts in the production of these effects is a difficult problem. Hazen and Klauder were the first in this country to publish their impressions and researches, and there is a rapid accumulation of material in the last few years in the German literature, which centers around the vagus-sympathetic system as the probable reaction mechanism, and the calcium potassium balance of the skin as a fundamental chemical fact in the production of cutaneous irritability. No doubt, too, the gastro-intestinal tract, whose susceptibility to emotion has recently been so beautifully summarized by Alvarez, is an important link in the sequence of events. The present status of knowledge is hardly much better defined than is that of the endocrin system, but the practical utility of calcium therapy and atropin suggests that there is some fire underlying all the smoke. There is not as yet any simple classification of all dermatoneurotics as either vagotonic or sympathicotonic, for it appears, according to Brill, that they may be either, and that they may be one thing with respect to their skins and another with respect to other groups of structures. It practice, however, it is usually easy to recognize the vagotonic, and he is the one, rather than the sympathicotonic, whom it is possible to help. The dermatoneurotic is not at all the nervous or outwardly emotional individual who finds relief in tears and screams. Such persons "blow off" and are relieved. The dermatoneurotic is controlled. His makeup, his "poker face" is perfect. He is the pillar of strength to whom all his friends and people come with their troubles. In storm he is calm, the master of every consciously controllable reflex, who never blenches before the blast. But for that perfect front, he pays, as I tell my patients, by an almost invincible predilection for "hollering down his backstairs." He sends outrageous, disturbing and contradictory messages to his sympathetic engine-room coördinating mechanism, by way of his

vagus speaking tubes. His is the inward tempest, the strife and struggle kept from the world. A little atropin, a little calcium, a few talks, a little physiotherapy, much rest and he can be transformed for the time being. Really to cure him may be the reëducational task of months.

Just how one recognizes the psychoneurotic background in the patient with a dermatitis it is a little difficult to say. There is an element of instinct in it, an appraisal of the small signs of tension that is done in part by the subconscious mind of the examiner. The vagotonic picture, or, perhaps, better, the disturbed vagus-sympathetic picture, is not hard to identify—the florid or flushing face; the moist, cold, perspiring, though red or bluish hands, the bright red line, or even wheal, that quickly follows a sharp stroking of the skin with a blunt implement (strich reaction). On this background, not alone urticarias and eczemas, but the dermatomycoses, thrive.

I see that I have read off the larger part of my page allotment without touching on the one most fascinating mystery, the one most intractable problem, and the one still simon-pure example of etiologically-defined constitutional eczema in the calendar. This is the eczema of the asthma-hay-fever complex, the so-called late eczematoid of Rost or prurigo of Besnier. The clinical picture is distinctive in the large majority of cases. Involvement of the face, especially the forehead and the skin about the mouth and chin, and of the flexures of the elbows and the popliteal spaces, by a dry, thickened, leathery dermatitis, excoriated by scratch, is highly characteristic. Bursting from time to time, without apparent excuse, into exacerbations which may convert the face into a shapeless and oozing mass with slits for eyes and mouth, and a "blob" nose; the scalp hair gummed with sticky exudate of a pallid, sickening, sweetish odor, the ears swollen and dripping, the neck fissured, the arms and the legs furiously itching and torn—the disease is one to terrify victim and onlooker alike. When the fundamental incurability of the process is taken into account, together with its hereditary background and its ability to injure personal appearance, which is the source of so much that is necessary in livelihood and essential in the happiness of life, you can easily understand why I rate diathetic eczema as one of the crippling ailments that affect mankind.

In the background lies always a certain group of perhaps etiologically important facts: (1) An inherited tissue irritability, an atopy as the students of sensitization phenomena call it, which makes the patient abnormally susceptible to irritants, or rather, makes substances irritants for him, or certain parts of him, that are not irritants for the normal individual; in some way his cellular constitution is at fault. (2) The group of predisposing causes already discussed as active in the simpler eczemas—the ichthyotic

and the seborrheic makeup, the focal infections, the gastrointestinal dysfunctions and the metabolic abnormalities. (3) Overshadowing in its fundamental character all the others is, in the opinion of recent writers, an abnormal nervous system. Just what makes these patients a distinctive nervous group is again hard to define. Yet their reactions are startlingly alike. In all there is an inward tension. There appears over and over the "electric relation" between parent and child. The youngsters are violently, almost unbalancedly active. They quickly get out of harmony with the established order and are vigorously "don't-ed" back into line. They are precocious often. As they grow older, they become destinationists, as I call them, rushing always upon an end, with that, and not the road, in view. The commonplaces of psychiatry, sex substitutions and fixations may be implanted upon this soil as on any psychotic background, facilitated by the sense of inferiority that life-long helplessness in the face of such an ailment brings about. Multiple sensitivity to proteins with which the patient may or may not have contacts is a recognized commonplace in such cases and is the despair of one who seeks in skin tests a clue to extrinsic etiology. There is some distinctive response in the few, none in the many cases, and the results of a general medical workup are equally disappointing.

The notion that blood chemistry will reveal much worth while is questionable, for the intimate chemistry of the skin is more probably the site of the disturbance, if any. There is no reaction to ingestion of urates (Michael). The acid-base equilibrium is disturbed. (Dromet and Verain.) The sugar-chlorid ratio changes, the sugar tolerance drops (Usher and Rabinowitz); the precipitable calcium decreases (Burgess), the calcium-potassium balance is disturbed with a rise in calcium on recovery from an attack, and the reverse during an exacerbation. An attempt is being made, as yet unevaluated, to attach most eczemas to the trail of arsenic, unwittingly ingested in a multitude of ways. Endogenous toxins from the intestine are blamed likewise. As Nathan and Stern assert, all these are probably but epiphenomena, and not centrally significant causative facts.

Summary of Treatment of Eczema. How shall we treat eczema? If I were asked, as I am, to give in a closing paragraph a scaling ladder to the outer confines of an unconquered citadel, I should say:

1. Search for the external excitant, though it may be difficult to find and its removal may avail little.

2. Reduce the carbohydrate intake. Take a meal-by-meal history of the diet.

3. Know and grease the ichthyotic.

4. Look for dermatophytosis of fingers, toes and groins and for pustules. Your patient's eczema may be an infection.

5. Try to restore balance by correcting the outstanding errors in focal infection and gastrointestinal troubles.

6. Expect less of sensitization tests, metabolism determinations, blood chemistry and routine physical and laboratory workups, and more from a full history, an experienced appraisal of type and quasi-empirical management.

7. Keep water and soap away, and learn to juggle ichthyol and tars, especially crude coal tar.

8. Use Roentgen ray sparingly, the quartz lamp often, autohemotherapy oftener, calcium in large doses on an empty stomach oftenest.

9. Study the nervous background, but do not fall back on its explanations until the physical person has been completely searched.

10. Pray—for we must, in this wilderness, as Ochsner from the depth of a vast surgical experience said, "leave something to God."

A CLINICAL STUDY OF MENINGOCOCCUS MENINGITIS.

An Analysis of 190 Cases Observed in a Period of Eighteen Months.

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Epidemic or meningococcus meningitis is a relatively uncommon disease which occurs both endemically and epidemically and is the main form of meningitis that occurs in epidemics. The only other type that may assume epidemic proportions is the pneumococcic form of the disease.

Epidemiologically this disease resembles poliomyelitis very closely as both are only mildly contagious. In an analysis of 500 cases of epidemic meningitis in New York, it was found by Neal that there were only 13 instances of more than one case in a household. This accords closely with the incidence in this series of 190 cases in which 5 instances of multiple cases were noted.

Epidemics seem to appear in cycles and in New York City these have been noted to occur about every nine to twelve years. This corresponds very well to our own experience in an analysis of cases that have been admitted to the contagious department of the Cook County Hospital.

In 1919, 43 patients with epidemic meningitis were admitted and in the succeeding years to and including 1926, the number of admissions was 16, 17, 9, 10, 9, 6 and 10, respectively.

This series consists of 190 consecutive cases admitted to the Cook County Hospital on the services of Hoyne, Bower and myself, from April, 1927 to September, 1928. Of the 190 cases, 132 (69.5 per cent) occurred in males, this being similar to the preponderance in the male of poliomyelitis and epidemic encephalitis. The youngest patient was three months of age and the oldest sixty-two years. There were 94 patients under fourteen years of age. It was thought best to include adults in this series for they constitute about a half of the patients and the symptomatology and therapy is practically the same as in children except for those under one year of age.

Headache, vomiting and fever were universal symptoms and rigid neck, Kernig and Brudzinski signs were found in every case except in infants under one year of age. Headache was not determinable in these cases and rigid neck, Kernig and Brudzinski signs were variable. Rigid neck was never present to the degree it is found in older children and adults, but existed in about one-half of the cases merely as an increase in resistance to anterior flexion of the head. In the other half of the cases in young infants, no rigidity was noted. Negative Kernig and Brudzinski signs were recorded in only 9 cases, all of whom were patients from three to twenty months of age.

Bulging fontanelle was observed in every case in infants whose fontanelles were still open.

The significance of positive cases of epidemic meningitis in in infants with absence of the pathognomonic signs of rigid neck, Kernig and Brudzinski signs is apparent and the unreliability of these signs is of extreme importance in dealing with young infants who have symptoms or findings at all suggestive of meningitis. Spinal puncture should be resorted to in any suspicious case even though the meningeal picture is not complete.

Convulsions were present in 12 cases (6.5 per cent), 6 of these being in patients under two years of age and the others in children four to eight years of age, except for one case which occurred in a boy, eighteen years of age. Those with convulsions ended fatally in 58 per cent of the cases in which they were observed.

Cases with petechiæ are considered the most severely toxic variety. Petechiæ were noted in 28, (6.7 per cent) of the patients and the mortality in these cases was 64 per cent, which was only 14 per cent greater than the general death rate (Table I).

Herpes labialis occurred in 19 cases (10 per cent) and was most frequent in the recovered cases. The observation that herpes frequently made its appearance several days after treatment had been instituted is undoubtedly the explanation for its frequency of occurrence in the cases that subsequently recovered, for many of the fatal cases might have developed herpes if they had lived long enough. Strabismus was present in 24 cases (12.5 per cent) and was

a slightly more common finding in the cases that ultimately recovered than in those that proved fatal.

TABLE I.—MORTALITY WITH REFERENCE TO SYMPTOMS AND COMPLICATIONS.

Symptoms and complications.	No. of cases.	Recovered.	Died.	Mortality, per cent.
Coma	39	12	27	69.1
Semicoma, stupor, drowsiness	29	19	10	34.5
Delirium	33	20	13	43.2
Convulsions	12	5	7	58.3
Petechiæ	28	10	18	64.2
Herpes	19	12	7	36.8
Chills	20	11	9	45.0
Strabismus	24	14	10	41.6
Ptosis	4	2	2	50.0
Unequal pupils	3	2	1	33.3
Nystagmus	7	6	1	14.0
Unilateral deafness	2	2	0	0.0
Bilateral deafness	8	8	0	0.0
Suppurative otitis	4	2	2	50.0
Arthritis	7	6	1	14.0
Iritis	1	1	0	0.0
Chorioretinitis	1	0	1	100.0
Encephalitis	1	1	0	0.0
Panophthalmitis	1	1	0	0.0

Ptosis was observed in only 4 cases, unequal pupils in 3, nystagmus in 6 cases.

Deafness was the outstanding sequela. It was recorded in only 10 cases (1.9 per cent); however, this number was considerably increased on reëxamination months after discharge from the hospital. The type of deafness was that of complete loss of hearing due to nerve involvement and in a few cases was noted at the onset of the infection while in others it manifested itself during the course of the disease. Recovery or even slight improvement in hearing was never noted after the deafness had once developed. In our records 8 cases were recorded as bilateral and 2 as unilateral before discharge from the hospital. None of these patients died. This observation was due undoubtedly to the fact that these patients were under observation longer and had a longer period than the fatal cases to develop this complication.

In only 4 cases was suppurative otitis media noted as a complication, 2 in patients who recovered and 2 in fatal cases.

One patient developed iritis, 1 chorioretinitis, 1 panophthalmitis, and 1 encephalitis in the convalescence from the meningitis in a case that ultimately recovered.

Patients with extreme opisthotonos in most instances had a clear mentality, because of the greater localization of the exudate at the base of the brain. These cases showed a prompt response to serum therapy and the prognosis was good.

The average stay in the hospital of the recovered patients was 19.6 days, the shortest period six days and the longest sixty-five days. The greatest number of patients, 22, or 23.6 per cent of the total, were discharged from the hospital on the fourteenth and fifteenth days (Table II).

TABLE II.—STAY IN HOSPITAL OF RECOVERED CASES.

Weeks	1	2	3	4	5	6	7	9
No. of cases	2	35	30	11	8	6	3	1

The mortality during the small epidemic of 1919 was 37 per cent and in the succeeding years 47 per cent.

The mortality in this series was 48.9 per cent. The epidemic began in April, 1927, when 14 patients were admitted, followed by a similar number in May, 12 in June and 5 or 6 in the months that followed. The mortality was highest under one year and over fifty years of age where it reached 87.5 per cent and 100 per cent respectively. The lowest mortality was noted between ten and twelve years of age where no deaths occurred. The youngest recovered case was that of a patient nine months of age and the oldest fifty years (Table III).

TABLE III.—MORTALITY ACCORDING TO AGE.*

Age in years.	No. of cases.	Recovered.	Died.	Mortality, per cent.
Under 1	8	1	7	87.5
1 to 2	12	5	7	58.3
2 to 3	4	3	1	25.0
3 to 4	18	15	3	16.6
4 to 5	6	4	2	33.3
5 to 6	6	3	3	50.0
6 to 7	5	1	4	80.0
7 to 8	9	6	3	33.3
8 to 9	2	1	1	50.0
9 to 10	6	5	1	20.0
10 to 11	5	5	0	0.0
11 to 12	3	3	0	0.0
12 to 13	4	2	2	50.0
13 to 14	4	2	2	50.0
14 to 20	39	24	15	38.2
20 to 30	25	11	14	56.0
30 to 40	13	4	9	69.2
40 to 50	13	2	11	84.5
50 to 60	7	0	7	100.0
60 to 62	1	0	1	100.0
Total	190	97	93	48.9

* The mortality is the lowest between the ages of 3 and 4, and from 9 to 12 years.

The mortality with relation to the state of consciousness on admission is a very important consideration since it may serve as an index of the prognosis. It was found that patients who were brought to the hospital in coma had a much smaller chance of recovery than those designated as semicomatose, stuporous or drowsy.

It was interesting to note that the duration of illness before admission was not as important a factor as is ordinarily believed. The patients who received treatment before the end of the first week of illness had a much better chance for recovery, however, than those who were ill seven days or more before treatment was instituted (Table IV).

TABLE IV.—MORTALITY ACCORDING TO THE DAY OF ILLNESS ON ADMISSION.

Day of illness on admission.	No. of cases.	Recovery.	Death.	Mortality, per cent.
First	20	12	8	40
Second	29	14	15	51
Third	30	20	10	33
Fourth	24	16	8	33
Fifth	4	3	1	25
Sixth	4	3	1	25
Seventh	8	3	5	63
Eighth	1	0	1	100
Twelfth	1	0	1	100
Fourteenth	3	1	2	66
Twenty-first	1	0	1	100

Failure to find organisms in a spinal fluid cloudy because of meningitis has been considered as circumstantial evidence in favor of the diagnosis of meningococcus meningitis. This was not well borne out by our observations, for in only 13 (6.76 per cent) were no organisms found. True, the meningococcus is not as abundant in a purulent spinal fluid as the streptococcus, staphylococcus or pneumococcus, but on careful search only in a few cases will one be unable to discover both intracellular and extracellular Gram-negative diplococci in material obtained by the first spinal puncture in a case of meningococcus meningitis. The picture is considerably altered as to the finding of organisms and the cell count after even one intrathecal injection of antimeningococcus serum.

The average cell count in the cerebrospinal fluid on admission was 11,780. The lowest count was 980 and the highest 90,000, in every instance showing a very definite polymorphonucleosis ranging from 75 to 96 per cent.

The fluid was cloudy on first examination in every case, but varied in degree from faint cloudiness to thickly purulent material that scarcely ran through the needle.

The globulin tests were universally positive.

The blood showed a leukocytosis in every case in which it was examined, the average being 23,700. The lowest white blood cell count was 11,200 and the highest 40,000.

Antimeningococcus serum of the polyvalent variety was used in the treatment of these cases. No difference was found in the therapeutic value of any of the brands employed, except that in a few instances definite improvement was not apparent until a change was made from one brand to another.

This brings up the question of how a more accurate and more scientific method of treatment could be established in this very serious disease. True, polyvalent serum is considered effective in the agglutination of all strains of meningococci, but it is reasonable to suppose that its efficacy may be more marked for one strain than another and the individual packages may also vary. A fresh serum may be more agglutinative for a particular strain than an older product. For this reason it is suggested that in the choice of a serum for a given case the agglutinating power be tested with the strain of organism causing the infection so as to employ the most specific serum. I hope to make this the subject of a report in the near future.

The average amount of serum used in recovered cases was 162 cc. intrathecally. The smallest amount in a case that recovered was 15 cc. intraspinally in two administrations and 15 cc. intravenously. The largest amount used was 495 cc. In 8 instances 50 cc. or less was sufficient to effect a cure.

Treatment consisted of the intraspinal injection of antimeningococcus serum immediately on admission and daily administration until the fluid became clear with a diminution of the cell count to a few hundred. With the improvement in the spinal fluid the clinical picture with relation to the meningeal findings improved and intrathecal injections were stopped. Daily spinal puncture drainage was continued, however, until the pressure returned to normal and the cell count returned to 100 or less. No serum was injected into these patients unless there was evidence of a recurring meningitis such as a reclouding of the spinal fluid or rigidity of the neck, Kernig or Brudzinski signs.

The largest amount of serum administered to a patient who died was 495 cc. given over a period of eighteen days with 15 cc. intravenously. This case was complicated by a preëxisting diabetes in a patient, aged forty-two years, who also showed a marked petechial rash.

Intravenous serum was administered to 68 patients, 39 of whom recovered, a mortality of 57.3 per cent, which is considerably higher than in the cases that were treated intrathecally only. The cases for intravenous therapy were chosen at random, this phase of the treatment depending mainly on the intern who first saw the

patient. The first intravenous serum injection was given at the time of the first intraspinal injection and subsequent injections were given at daily intervals along with the intrathecal injections. One dose of intravenous serum, 15 cc., was administered to 11 of the recovered cases, two doses to 11, three doses to 7, four doses to 2, five doses to 2, six doses to 3, ten doses to 1, and twelve doses to 2 (Table V).

TABLE V.—INTRAVENOUS THERAPY IN RECOVERED CASES.

Number of injections	1	2	3	4	5	6	10	12
Number of cases	11	11	7	2	2	3	1	2

The average number of spinal punctures in the recovered cases was 8.1. The smallest number was 2 and the greatest number 30. The greatest number of spinal punctures in a case that finally succumbed was 20.

Complications after or attributable to spinal punctures consisted only of the appearance of chills followed by collapse in 6 cases, in 5 of which intravenous-serum therapy had previously been used.

Serum rash, which made its appearance from the seventh to the twelfth day, was present in 26 cases, in 17 of which intravenous-serum therapy had been used. This reaction occurred equally in the recovered and the fatal cases. One patient developed a severe serum reaction on the twenty-eighth day after treatment was instituted. This patient was first given intravenous serum on the seventh day and received in all 135 cc. intravenously.

Cisterna punctures were performed in 12 instances. This procedure was resorted to only if the opisthotonus was so marked that sufficient flexion of the back was not possible to permit of spinal puncture, or if sufficient fluid was not obtainable by spinal puncture due to obstruction in the spinal canal by organization of the exudate. Four of these 12 patients recovered after two or three cisterna punctures.

The average cell count of the spinal fluid obtained two to five days before discharge from the hospital was 49 cells per c.mm. In no instance was the cell count found to be below 12. The type of cells was not noted.

The follow-up on these cases consisted of the reëxamination of 61 of the recovered patients from two to sixteen months after discharge from the hospital. The remaining 35 patients we were unable to locate.

Of the 61 patients, 34 (55.7 per cent) were entirely free from complaints and in many instances told of feeling much better than before the onset of the illness. In this number there were two children whose mothers reported an improved mental condition since the illness.

The outstanding sequela was deafness, which occurred in 16 (25.4 per cent). Twelve of these patients had a bilateral total deafness while the other 4 had complete loss of hearing in only one ear. In 2 instances the deafness did not make its appearance until two and a half and three months, respectively, after discharge from the hospital. Both of these were bilateral cases and the patients had normal hearing on discharge from the hospital. This could be explained only by scar-tissue contraction about the eighth nerve resulting in atrophic nerve changes.

Lumbar pain was the next most frequent complaint and occurred in 8 cases (13 per cent). It was generally described as an occasional pain at the site of the lumbar punctures, but 2 patients complained of severe, agonizing pain on bending the trunk forward.

Next in frequency was vertigo, which was complained of in 5 cases; 4 of the patients described it as slight while one told of marked dizziness followed by falling, but never accompanied by loss of consciousness.

Generalized weakness was noted in 3 cases, and described as a tired feeling and indisposition to be as active as previously.

Aching of the legs was complained of by 3 patients, all of whom also experienced lumbar pain.

There was one case of impaired mentality in which the mother noted the child's inability to learn at school.

One patient developed swelling of the left leg which disappeared on rest in bed and recurred on the resumption of the upright position. This was apparently due to thrombosis of the large veins.

Only one patient complained of headaches, which were not very severe and occurred only occasionally.

Strabismus was noted in only one case although it was observed in 14 recovered cases during the patients' stay in the hospital. This shows a marked tendency for improvement in eye complications.

One patient complained of anorexia while 3 told of an increase in appetite.

One case is worthy of special mention because of the very unusual sequences of events in the course of the illness.

Case Report. In March, 1928, the patient, a woman, aged twenty-two years, entered the hospital with a typical case of epidemic meningitis that responded in the usual manner to serum therapy. The patient left the hospital in good condition sixteen days after admission. Two weeks later she returned to the hospital with the complaints of headache, dizziness and vomiting. There was no neck rigidity, Kernig or Brudzinski signs. The vomiting was severe and responded only to a very rigid dry diet. The diagnosis made at that time was postmeningitis cerebral irritation and starvation acidosis. No spinal punctures were done at that time and the patient recovered except for a slight dizziness and left the hospital in six days.

Eight months later she again entered the hospital with the complaint that for several days she had had a "head cold" and for the past two days severe headache and vomiting with dizzy spells and generalized aching. At this time there was only slight rigidity of the neck and the Kernig and Brudzinski signs were negative. Spinal puncture was performed and cloudy fluid under increased pressure was obtained. Meningococci were discovered in the smear and there were 15,000 white cells per c.mm.

On the second day the patient showed marked rigidity of the neck with a positive Kernig and Brudzinski sign and only 5 cc. of fluid was obtainable on spinal puncture, but 35 cc. was obtained on cisterna puncture. Cisterna puncture was then performed daily for the next four days with the introduction of 30 cc. of antimeningococcus serum and the patient left the hospital cured in nineteen days.

Just what lesions existed during the eight-month interval is mere conjecture but the first return to the hospital spoke for some cerebral irritation and the only possibility for a focus to remain quiescent and then be reactivated after eight months would be for it to have been localized somewhere in the spinal canal, as in the cervical region. The failure to obtain much fluid on spinal puncture would speak for a partial block in the spinal canal below the cisterna magna.

Then again one cannot exclude the possibility of a reinfection, but the return of the symptoms of headache and vomiting two weeks after the patient's first discharge from the hospital leads one to believe that the meningeal process was active at that time.

The absence of meningeal symptoms on the first examination during the second attack would speak for a localized spinal meningitis and dissemination to the cerebrospinal meningitis after intrathecal serum administration.

Summary. A report is made on 190 cases of meningococcus meningitis observed in a period of eighteen months at the Contagious Division of the Cook County Hospital.

The analysis includes a report of multiple cases in one family, the average stay in the hospital of recovered cases, the age frequency, the mortality according to age, the clinical picture, the day of illness that treatment was instituted and the type and rationale of treatment employed, the complications with relation to their frequency and prognostic value, the spinal-fluid findings, the cisterna-puncture results, and the reports of reëxaminations made months after the patient's discharge from the hospital. The occurrence of deafness two and a half and three months after discharge from the hospital deserves special emphasis. Finally, the absence of meningeal symptoms in infants and the apparent futility of intravenous serum therapy are noted.

THE LARGE BOWEL IN CHRONIC ARTHRITIS.*

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This communication has to do with the incidence of the abnormal variations in shape and size of the colon in chronic arthritis and the changes which may take place while the patient is under dietetic treatment.

It is not a new observation that these disturbances occur in chronic arthritis, although they have been largely of surgical interest. Goldthwaite and Osgood pointed them out and, in treatment, applied various orthopedic measures. Lane associated arthritis with intestinal stasis, which he believed due to membranes or kinks. He and others reported improvement, and even cure, with colectomy and with plastic operations. However, due apparently to the general belief in the infectious etiology of arthritis, this aspect of the disease has received little attention.

These colon lesions may have another significance. In monkeys fed with autoclaved diets, McCarrison produced changes in the colon which he described as a "ballooning of the large bowel and a tissue-paper-like structure of the viscus." From his investigations on experimental animals, he concluded that atony of the human colon is the result of malnutrition.

It is well known that variations in diet and states of nutrition influence the course of chronic arthritis. For years Pemberton has insisted on this, and has treated many cases of arthritis with low-calorie diets, restricting carbohydrates especially. Some years ago we had occasion to stress the importance of balance in the diet between carbohydrate, protein and vitamins; others, notably Rowlands, associated the disease with vitamin deficiency.

In a series of 60 patients with chronic arthritis the large bowel has been examined by Roentgen ray following a barium enema, and changes which we considered abnormal were observed in 65 per

* Read before the meeting of the Association of American Physicians, Atlantic City, May, 1929.

cent of these cases. The Roentgen ray picture shows changes in tone, haustral markings and length. Atony is sometimes seen throughout the entire colon, or more frequently it is confined to the cecum where it may be extreme. Haustral markings, in the atonic areas, are usually absent or much decreased, and this decrease in haustration may extend throughout the large bowel. The length of the colon may be so increased as to result in change of shape or even extensive looping and redundancy.

This Roentgen ray picture has been studied from time to time while the patient has been on dietetic treatment, and it has been found that the colon assumes a more normal appearance. Most effective results have been observed with the use of diets high in vitamin and low in carbohydrate. The antineuritic vitamin has been given freely in the form of baker's yeast or wheat germ. As a rule, the calories were restricted to some extent.

The illustrations show how much change may take place. The tone of the cecum sometimes increases very much, and there is almost always well-marked increase in the depth and regularity of the haustral markings. Usually the colon becomes shorter; the looping and redundancy may disappear. The transverse colon becomes straighter, giving the colon, as a whole, an H-like appearance.

Many patients have been observed now for some months' time. In practically all improvement has been noted in the Roentgen ray appearance of the colon. This improvement may continue for several months' time while the patient is on a diet high in vitamin and low in carbohydrate. As a rule, the patients are much benefited by this dietetic treatment, sometimes very much so. Observations have been made on patients suffering from rheumatoid-arthritis and from osteoarthritis. On the whole, better clinical results have been noted in the rheumatoid group.

These observations are offered to support the belief that nutrition and chronic arthritis are related. Such a belief is not opposed to the general view that chronic arthritis is of infectious origin. Deficiently fed animals are highly liable to infection and infection may complicate or be part of a deficiency syndrome. In many of the cases studied focal infection was present. It may be that malnutrition creates a state favorable to the development of infection. In some cases the bowel itself may be the source of the infective or toxic agent causing the disease.

The value of carbohydrate restriction in arthritis may also be explained on these grounds. Carbohydrate favors the development of deficiency disease and with vitamin B restriction it is difficult to produce the deficiency disease unless carbohydrate is given in excess, as, for example, polished rice. In our clinical observations we have found carbohydrate reduction an important part of this dietary treatment.

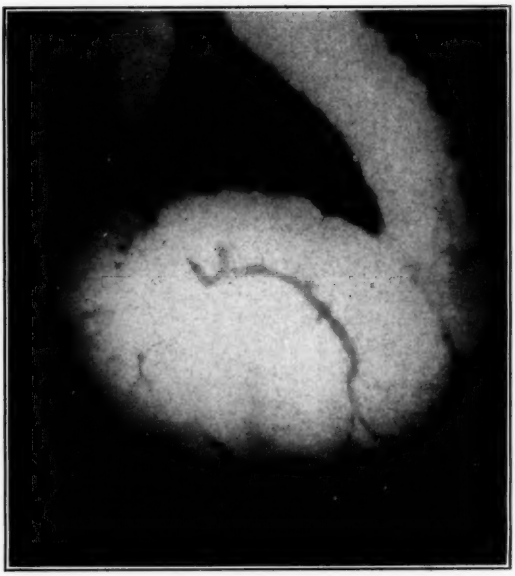

FIG. 1

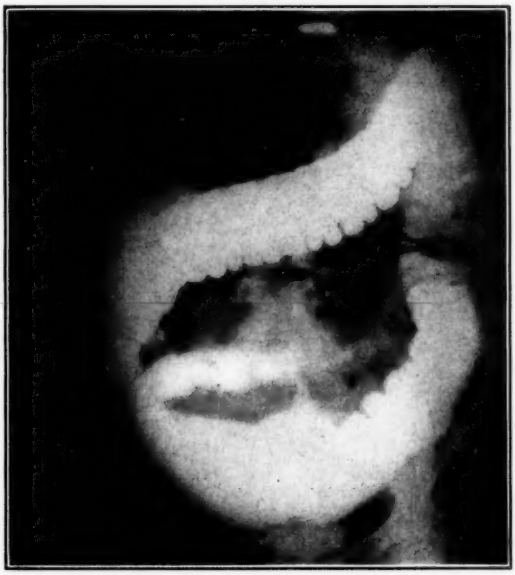

FIG. 2

FIGS. 1 and 2.—Miss C., aged seventeen years. Pain and swelling of the metacarpal phalangeal joints for ten years. During the summer of 1928 arthritis developed in knees, ankles and shoulders. No history of sore throats, no focus of infection found. Admitted to hospital, September 29, 1928, showing moderately severe arthritis of rheumatoid type and also aortic and mitral valve lesions. Changes are shown which occurred in the colon over four weeks of dietetic treatment. Much clinical improvement observed while patient was under this treatment.

FIG. 3

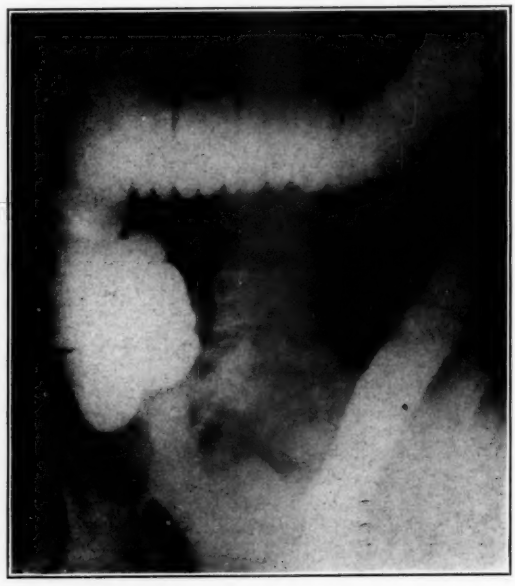

FIG. 4

FIGS. 3 and 4.—D, aged forty-four years. Rheumatoid arthritis of one year's duration. History of obstinate constipation. No focus of infection found. Recovery while under dietetic treatment. Above changes in the colon took place over two months.

FIG. 5

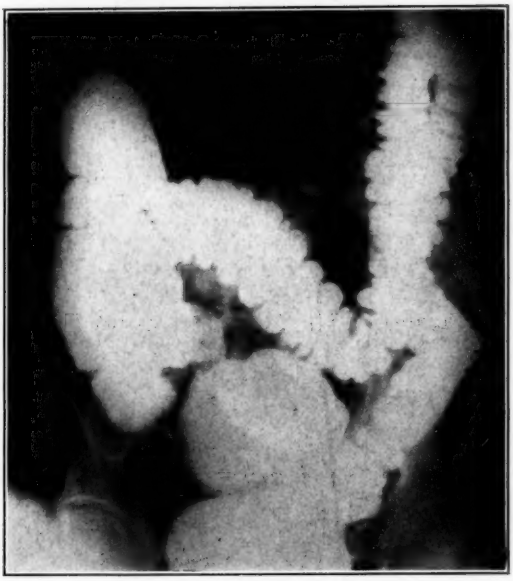

FIG. 6

FIGS. 5 and 6.—Mrs. S., aged thirty-five years. Severe rheumatoid arthritis for four years. For many years has had a discharging middle ear. Above changes took place over one month of treatment with diet.

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Conclusions. 1. It is believed that the abnormalities observed in the colon in arthritis are manifestations of malnutrition.

2. Malnutrition frequently plays a part in the development and course of chronic arthritis.

3. The abnormalities found in the colon are markedly improved by dietetic treatment with coincident improvement in the arthritis.

THE USE OF DEXTROSE IN PNEUMONIA.*

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It is our purpose to present some clinical observations which we have made during the past four years on the use of dextrose in the treatment of pneumonia. It is our belief that it is of value, but we also know from our observations that this procedure has definite limitations. Further, we are aware of the danger of suggesting another form of therapy, which we may regard as beneficial, in a disease such as pneumonia.

In any discussion of pneumonia, particularly in reference to therapy, it should be defined as clearly as possible as to whether the cases in question are toxic or nontoxic pneumonias. It is a common experience to observe both forms in almost any pneumonia service during the season when this disease is prevalent. They have an entirely different prognosis. Further, it is also important to know, when speaking of this disease, what is the usual mortality in the community: is there a great deal of pneumonia with a high death rate or are there very few cases and a low death rate? In such a community as the former, therapy in the toxic case is a great problem; while in the latter, treatment is a more simple matter. Pneumonias in children should not be considered with the adult form, nor do we include any postoperative pneumonia. In other

* Read by title, Association of American Physicians, Atlantic City, 1929.

words, in order to estimate the therapeutic value of any method of treatment, particularly in a disease such as pneumonia with its variable virulence, it is most important to judge the results from those cases which are toxic and likely potential fatalities, rather than from the mild forms which have a higher percentage of recovery. It is granted that one cannot always differentiate these forms, but we believe there are some definite points which can separate them fairly well. Nontoxic cases may later become toxic; in fact, the majority of pneumonia patients for the first three days are not obviously toxic. Naturally, there are exceptions as when toxicity is present almost from the onset of the infection. We see many of this character. In communities which have pneumonia with a high mortality, and particularly if such a condition has been almost a fixed problem in that it repeats itself year after year, there is a tendency to accept the mortality as unalterable and possibly become fatalistic in attitude, or certainly nihilistic, as far as therapy is concerned. On the other hand, the opposite attitude also occurs, for in what disease have we used more drugs than in pneumonia? Have we not had the opportunity year after year to observe the valuelessness of certain drugs in our fatal cases, and at the same time note the nontoxic case recover without any particular therapy? Such clinical observation has been common knowledge for many years.

Pneumonia has been a reportable disease in Pittsburgh for the past four years, averaging about 3300 cases yearly, with a mortality a little over 40 per cent. McMeans has reported the following percentages on the serologic types of the infection observed in Pittsburgh (2998 typings): Type I, 17; Type II, 14; Type III, 14; Type IV, 53. It is, therefore, obvious that the usefulness of serum is markedly diminished in view of the small number of Type I cases. Further, probably one-half of these cases are not admitted to the hospital until after the third day, thus adding another disadvantageous factor to the giving of serum. Type III and some of the Type IV cases appear to be the most virulent clinically. Robinson has noted this in our pneumonias and also has found that Type IV can be subdivided into a few groups. Cooper, Edwards and Rosenstein have recently written on the same subject with reference to the New York cases. They noted that Type IV contained a number of fixed subgroups. It is to be hoped that in the future an effective polyvalent serum may be available along the lines of Felton's serum as recently reported by Park and by Cecil. In the meantime other methods should be tried, and it is really for this reason we have been interested in the use of dextrose. At the present, as far as our own problem is concerned, there is no available specific drug or polyvalent serum.

Randolph has recently reported on certain features of pneumonia in Washington, D. C. He believes that Streptococcus hemolyticus

is the common etiologic factor in their clinical problem. The pneumonia in Pittsburgh is pneumococcic in most instances. We see Streptococcus hemolyticus in a certain number of the empyemas, but whether this indicates absolutely that the original infection (pneumonia) was also the same may be difficult to say, although it is likely that it is the same organism. We have never seen a blood culture in pneumonia showing Streptococcus hemolyticus. It is always pneumococcus, and blood culture findings are more accurate than those of the sputum. Possibly in streptococcic pneumonia a bacteremia is not common. Further, in our observations, in case an empyema developed in a patient who had had a positive pneumococcic blood culture, the organism was the same in the pus from the chest. We regard most of our pneumonias as bronchopneumonia and that much of the lobar distribution is a manifestation of a coalescing process. Is it not possible that the terms "lobar" and "broncho" have outlived some of their usefulness, and that we should think more in terms of toxic and nontoxic pneumonia? During the four-year period in which these cases were studied we have noted that our pneumonia has slightly changed with regard to its time of appearance. December, January and February were formerly our most active months, but in recent years, during March, April and May, most of the infection has occurred. Last year May showed the greatest mortality. We do not include in this the influenza epidemic of December, 1928, when a great deal of pneumonia was seen. It may also be stated that our pneumonia is present every month of the year, few cases, of course, in the summer, but often these cases carry a very high mortality.

In our treatment of pneumonia we have used what is generally regarded as the proper symptomatic procedures of therapy, from mustard plasters locally to the use of oxygen by the mask method. We have not had the opportunity of using the Barach tent. Naturally, with an infection of known high mortality, an ample opportunity to test out any method on toxic cases has been afforded. We have long since lost all faith in the effectiveness of digitalis and oxygen as life-saving measures in toxic pneumonia, although we know that the latter gives symptomatic relief and have seen isolated instances, very few in number, when it appeared to be life-saving. Symptomatic relief is not enough as a therapeutic test in a disease such as pneumonia, and symptomatic relief in nontoxic cases and toxic cases in the end is quite a different problem. We do not think the other details of treatment merit any particular mention, save to say that we regard pituitrin, atropin, morphin and occasionally caffein as of value, but we have never been impressed with alkalies, especially sodium bicarbonate. Moderate dosage of potassium citrate (30 grains, q.i.d.) we often use in a routine way. It is taken for granted that fluids are forced, and that nursing, perhaps the most important factor, is efficiently carried out from the onset of the disease.

As we have referred especially to toxicity, it might be well to attempt to give our criteria of such a state. Naturally, there is bound to be a personal factor involved for what is a toxic case to one may not be so to another. With this in mind we have tried to estimate this very important state of the patient from signs which we believe from experience to be reasonably certain. We realize, of course, that one can never be too sure of clinical signs, as different individuals may react in atypical ways. However, there are two points to which we wish to call attention. A pulse rate of 120 or over, not immediately following any movement or exertion in bed or any excitement, such as a physician coming into the room, that is constant at almost any stage of the illness usually means a toxic case in our pneumonias. This is especially true if it has been gradually rising and the closer it gets to 140 the more likely is the case to be a fatal one. In our judgment this is the most sensitive guide to toxicity in the pneumonias that we see in this community. The second factor is a positive blood culture. Pneumonia with a pneumococcus in the blood, irrespective of community, carries a very high mortality (Cecil, 78 per cent; Cole, 67 per cent; our first series, 73 per cent). We have seen occasions in the past where the usually virulent Type III appeared to be very mild even in the presence of a positive blood culture. This, however, is only the isolated observation. The number of pneumococci in the blood, as pointed out some years ago by Sutton and Sevier, and later by many other observers, is probably of much importance, the greater the number of colonies the higher the death rate. Blood culture studies on pneumonia are very valuable, and during the past year we have, at times, repeated them to find an early negative and a later positive result. All toxic cases with a negative blood culture should have second cultures, if possible during the last twenty-four to forty-eight hours of their illness, as it is probable that a higher percentage of them will show a bacteremia. Richey and Goehring, in our laboratory, noted that in agonal blood cultures on patients dying from a pneumonia, terminal or otherwise, pneumococcus was found in 50 per cent. As some of these pneumonias were post-operative or terminal factors in chronic conditions, it may be that in pneumonia as a primary disease the number would show a higher percentage. From our own results the type of case upon which we wish to have more accurate information, we repeat, is the fatal one carrying a negative blood. Our figure of 32 per cent mortality for negative blood culture cases (see Chart IV) is very high, although our percentage of positive cultures, about one-third of the cases, agrees with the number reported elsewhere. In Cole's studies 343 cases of lobar pneumonia in which blood cultures were negative showed a death rate of only 11.6 per cent; while in 119 cases in which the blood cultures were positive the death rate was 67.1 per cent. Repetition of the blood culture as was done by Sutton and Sevier

will likely demonstrate that a certain number of negative cases will later be positive, particularly if they are toxic ones. By this method they showed in 43.8 per cent of their cases a positive blood at some stage of the disease. This has also been noted by others (Cole, Cecil, Irons), and we have as previously stated, made the same observation. In none of our cultures have we attempted to estimate quantitatively the pneumococcus present. This would add valuable information, even though it entails a good deal of extra work for a routine study.

The first report on the use of dextrose in pneumonia was by a French writer, Enriquez, in 1914. He gave a 25 per cent solution intravenously three or four times a day in 250-cc. amounts and reported that good results were observed. In this country in the same year Litchfield made a similar report, using dextrose in practically the same way as had Enriquez. Both of these writers believed that dextrose was of value as a food and as a stimulant to the heart. There were no further observations until the influenzal epidemic in 1918. At that time John, Wells and Blankenship, and Koons reported favorably on its use in pneumonia. Ten per cent solution given intravenously two or three times per day was the usual method employed by these writers. Two English workers, Bennett and Dodds, in 1925, gave from 200 to 500 gm. of dextrose by mouth in lemonade in each twenty-four-hour period and they believed it to be of value in the pneumonias which they studied. Bollman, Hummel, Prisbram, Pfalz, Hay, Stejskal, Johnston and Mitoldschey have also mentioned that dextrose is of value in pneumonia and in toxic conditions. The experimental studies of Edmunds and Cooper on the toxic myocardium showed that dextrose solution given intravenously had the power of restoring the heart beat when all other measures failed. It was this work that induced us to use dextrose in the toxic cases of pneumonia, and we were impressed with the results during the first year of trial. Most of the German literature has been in reference to the relation of dextrose to the heart following the work of Budingen, who believed that intravenous dextrose was of value in angina pectoris. Klewitz opposed this view, but Jagic and Klima, Meyer and Hess confirmed Budingen's work. These latter observers believed that the action of digitalis was improved following the use of dextrose. One of us (Lynch and Webster) has already reported a series of pneumonia cases in which the favorable effect of dextrose solution intravenously was noted as compared with control cases under digitalis therapy.

At the present time, in our opinion, the best way of giving dextrose in a case of pneumonia is as follows:

1. From 400 to 600 gm. of dextrose are given by mouth per day. The most practical method of accomplishing this is to dissolve 200 gm. of dextrose (Dextrose Powder—Corn Products Company) in 1000 cc. of water, to which is added the juice of 2 or 3 lemons.

The liter thus contains 800 calories. It is very palatable, and we try to have the patient drink from 2 to 3 liters each twenty-four hours (1600 to 2400 calories). It is given frequently in small quantities during the time the patient is awake. If too sweet for the patient add more water or regulate according to individual taste. All cases are treated this way from the earliest time possible in the disease. We have noted that pneumonia cases having private nurses have much less difficulty in taking over 2000 calories per day by this method than do the ward patients. Good nursing, therefore, is very important with reference to this particular phase of treatment; in fact, it is essential. At times, patients seem to be quite unable to take the dextrose lemonade on account of the nausea and vomiting which is occasionally seen early in the disease, and also after taking large amounts for several days the stomach becomes irritable and further ingestion is difficult. We have tried other vehicles for dextrose, but have not been very successful. Williams and Pfluke have informed us that they have had no difficulty in giving 2000 to almost 3000 calories per day of dextrose in this way.

2. When it is impossible to give dextrose by mouth in a sufficient amount or when the case appears to be toxic, a 25 per cent solution of dextrose is given intravenously four to six times each twenty-four hours. The quantity injected never exceeds 200 cc. at one time. It must be given slowly, at least one-half hour for the injection. We find that in very toxic cases it is often impossible to get the patient to drink any satisfactory quantity of the lemonade, hence the intravenous method is necessary. By this method from 800 to 1200 calories can be given daily, in addition to a similar number by mouth, if possible. It is most important that increasing toxicity, even when the patient is taking dextrose satisfactorily by mouth, be met in this way as early as possible. This measure is of no value in moribund cases. One may add that 50 per cent dextrose solution may be used intravenously.

According to our charts, we have divided the cases into two groups as regards dextrose treatment, namely, adequate and inadequate. This grouping is not always easy to define but we are attempting to reach some quantitative factor so that results can be more easily read. As with any drug or serum, a sufficient dosage is essential for therapeutic effect. Our present conception of adequate dextrose treatment is, at least, 400 gm. of dextrose by mouth per day, or when given intravenously, at least 200 gm. (50 gm. four times a day). It is the total caloric intake that counts, whether by mouth or vein, and the closer one gets to 2400 calories per day, the better.

We are inclined to feel that the main value in dextrose is in the additional freely available calories of carbohydrate, as was mentioned by Enriquez and Litchfield, and as Meakins has so well stated, "I am convinced that in pneumonia, for the prevention of

cardiac failure, it is essential to maintain the carbohydrate and glycogen reserves by the intake of relatively large amounts of glucose. This is accomplished by the administration of copious quantities of fluid and carbohydrate, intravenously, if necessary, early in the disease, and not when the patient is *in extremis.*" According to Du Bois, pneumonia is associated with a 20 to 50 per cent increase in metabolism. The 1200 to 2400 calories of food given by this method should, at least from the physiological point of view, be of value, and may be the deciding factor in recovery. It is a common observation to notice a better pulse after intravenous dextrose. Whether this is due to any direct action on the heart or not we do not know. Edmunds believed possibly there was a direct action on heart muscle; however, it may act indirectly by improving general nutrition, as suggested by Meakins. It is our impression that in a toxic case we see more improvement in the patient's condition from the same number of calories given intravenously than by mouth. We speak of pneumonia as being a self-limited disease, and if the patient is able to hold out for sufficient time, enough antibodies will be formed so that recovery takes place. Possibly dextrose acts entirely in helping the patient "go the distance," or, in other words, it supplies the individual with the nutrition with which to fight the infection. In the past nutrition has been a problem, as the toxic pneumonia cannot take food in a satisfactory amount. Milk and its preparations do not appear to be easily handled by the sick pneumonia patient. When solid and liquid food is taken freely and easily, in our experience it usually means a very mild infection, and these cases do not make up our high mortality lists. For this reason, in the recent past our teaching has been to give an abundance of water, but no solid, even if light food, to the toxic case. It is in this regard that dextrose is so valuable, a high caloric intake can be readily maintained without much difficulty. Erlanger and Woodyatt have shown clearly the pharmacologic action of dextrose and how much of it can be metabolized. There are certain practical advantages in the method here suggested. It is easily carried out, and, therefore, can be used readily by the practitioner at the onset of the disease. On the other hand, cases seen in hospital practice are often more advanced and intravenous therapy may be the only method possible to use. This procedure is not difficult to perform in a hospital, but it is quite difficult in private practice. We have not used the subcutaneous method of giving dextrose, although it is accepted that it is of value. We have always felt that it disturbed the patient too much. Dextrose by bowel is not of much value in this disease as the caloric intake is too small.

In the earlier years of this work, we now feel, dextrose was in the main incorrectly used. It was only given intravenously to the toxic cases, but now patients can take it by mouth at the onset of the

infection, and perchance, some of them who later would otherwise become seriously toxic may be saved from going into that state. It is a very difficult matter to be certain about this, as we have observed cases become very toxic when taking from the beginning a goodly number of calories by mouth. However, we feel that it is a good practice to follow and certainly on a physiologic basis. Further, in the past, we were inclined to wait too long or the patient was too long in a toxic state before giving intravenous dextrose. It must be given earlier, and it is useless when the patients are moribund. Also, we did not give dextrose frequently enough or in a sufficient strength. Twenty-five per cent four times a day is better than 10 per cent twice a day as was our former practice, and an intake of 600 gm. by mouth per day is better than 200 gm. per day. Early in its use we stopped giving larger amounts than 200 cc. intravenously, as we observed evidences of reactions and circulatory embarrassment with larger quantities as Clark, Robertson, Oliensis and Stern had noted. Venous pressure records were made in cases receiving intravenous dextrose solution, using the instrument and technique of Hooker and Eyster. The venous pressure was used to detect circulatory embarrassment which might result from the addition of fluids to the right side of the heart. An increase in pressure above normal was an indication to reduce the amount of fluid given per dose. Frequently venesection was resorted to before giving dextrose intravenously in cases with an increased venous pressure. By this method the danger of producing circulatory failure by intravenous injection is minimized. This work will be reported separately by one of us. Chills have been noted after the injection at times. Since we have put one person in entire charge of the preparation of the solution, the reactions have been reduced to a minimum. In patients beyond middle life we have occasionally seen a reaction which seemed to be harmful, and in this type of patient care should be taken against a repetition, because if a second reaction occurs we do not continue the intravenous method of therapy.

The clinical improvement we have noticed in the cases that respond is definite. The pulse is stronger and slower, and the patient looks less toxic. We would emphasize, however, the pulse rate as the most important guide as to prognosis. We are not overly impressed by the importance of blood-pressure readings, although it is generally admitted that a falling pressure is not a good sign, but a normally low pressure even under 100 may be quite compatible with a mild or toxic pneumonia and recovery. Newburg and Minot, some years ago, referred to this, and we agree with them. In our opinion, the blood pressure is undoubtedly of less value than the pulse rate as an index of prognosis. The white cell count rises as improvement occurs, unless the count was a high one at the beginning. We have at times seen a count of 4000 to 6000 increase

to 20,000 in two days, and frequently observed lesser rises. Sugar may appear in the urine in small amounts, but when the administration of dextrose is properly spaced this can be avoided.

CHART I.—1925 TO 1928.

Mortality of Cases Treated with and without Dextrose.

	No. of cases.	Mortality percentage.
Dextrose treated	74	60.8
No dextrose	86	27.9
Total	160	43.1

During this period only the more toxic cases were treated with dextrose, and in nearly all the intravenous method only was used. Further, it was rarely given more than three times daily. Very few of the above cases we would now consider as having been adequately treated.

CHART II.—1925 TO 1928.

Analysis of Mortality in Dextrose-treated Cases. (74 *Cases with* 60.8 *Per Cent Mortality.*)

1. 48.8 per cent had one day of treatment
2. 22.4 per cent had two days of treatment.

71.2 per cent had not more than two days' treatment.

This group of fatal cases included many that were moribund or treated late in the disease. Almost three-quarters of the cases received less than three days of treatment. This is due to the fact that only the more toxic patients were treated, and frequently the beginning of treatment was too long delayed. The intravenous method only was in use over the greater part of this period, and represented much smaller amounts of dextrose (in grams) than we now use.

The high mortality in the positive blood culture cases is to be noted, also the relatively high percentage in the negative cases. There is nothing to indicate a favorable action of dextrose in this chart.

We would call attention to the comparison between the mortality in the positive blood-culture cases in Charts III and IV, and also to the difference between the adequate and inadequate treatment results in Chart IV. Moribund patients are included in all charts, and this probably accounts for the very high mortality percentage in the positive blood-culture group with inadequate treatment. The cases without blood cultures are merely included to indicate the severe form of infection that we see, many being in the hospital only for a short period of time. The age mortality agrees with the observations of Fergusson and Lovell who have recently studied the pneumonia in Manchester, England. It is possible that the high mortality in the negative blood culture cases is an index of the severity of the pneumonia in this community.

CHART III.—1925 TO 1928.

Pneumonia Mortality in Relation to Blood Cultures.

Blood cultures taken	72
Blood cultures positive	19 (26.3 per cent)
Blood cultures negative	53 (73.7 per cent)

Mortality in Positive Blood Cultures.

	Cases.	Per cent.
Died	14	73.7 (12 had dextrose)
Recovered	5	26.3 (2 had dextrose)
Total	19	

Mortality in Negative Blood Cultures.

	Cases.	Per cent.
Died	16	30.2 (12 had dextrose)
Recovered	37	69.8 (16 had dextrose)
Total	53	

CHART IV.—1928 TO 1929.

Pneumonia Mortality in Relation to Blood Cultures.

	Number.
Cases	126
Deaths	53
Mortality	42 per cent
Blood cultures taken	97
Positive blood cultures	29 (29.7 per cent)
Negative blood cultures	68 (70.3 per cent)
Cases without blood cultures	29

Mortality Percentages.

	Per cent.
Patients with positive blood cultures:	
29 with 15 deaths	51.7
17 with adequate dextrose, 5 deaths	29.4
12 with inadequate or no dextrose, 10 deaths	83.3
Patients with negative blood cultures:	
68 with 22 deaths	32.3
43 with adequate dextrose, 8 deaths	18.6
25 with inadequate or no dextrose, 14 deaths	56.0
No blood culture taken:	
29 patients with 16 deaths	55.1
3 patients with adequate dextrose, 1 death	33.3
26 patients with inadequate or no dextrose, 15 deaths	57.6
Mortality with reference to age:	
Cases under forty years (55 per cent)—mortality	20.0
Cases over forty years (45 per cent)—mortality	64.0

Summary. In the treatment of pneumonia, particularly of the toxic forms, we have described a method whereby it is possible to maintain a high caloric intake of food in the form of dextrose lemonade by mouth and hypertonic (25 per cent) dextrose solution intravenously: 2400 calories per day may be given. The nutritional value would appear to be the most important factor in this form of therapy, but there are clinical signs of an improved circulation after the intravenous therapy which might indicate a direct action on the heart muscle. The method of treatment is a physiologic one, and in the advent of an effective available polyvalent serum may still

be of value as a supporting measure in treatment. This form of therapy has previously been described, but for some reason has been discontinued. From our limited experience stated above, we would recommend a further trial of this method, and would suggest that its value be estimated from the results seen in those pneumonia cases which have a bacteremia, and which are given an adequate therapeutic test.

In our first series of 160 cases for 1925 to 1928, as indicated in Charts I, II and III, dextrose was given only in small amounts intravenously and only to the toxic cases. This accounts, we believe, for the marked difference in the result as seen in our second series 1928-1929 of 126 cases which occurred in a year when the general mortality was the same. In the second series, dextrose was given much earlier in the disease and in larger quantities both by mouth and by vein when necessary.

Positive blood-culture cases in the second series showed a 22 per cent lower mortality than in the first series. Moreover, the number of cases in the second series was larger.

There is a definite lowering of mortality as seen in Chart IV in all groups of cases which received adequate dextrose treatment.

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THE PATHOGENESIS AND TRANSMISSION OF TUBERCULOSIS.*

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We are, I believe, gradually acquiring a conception of tuberculosis that explains many obscure aspects of its pathogenesis and promises to modify profoundly procedures for its control. Briefly stated it is that tuberculosis of early life has the characters of a first infection, whereas tuberculosis of later life is a disease modified by acquired immunity. This conception though obviously not new is just beginning to find its way into textbooks of medicine and pathology and has had almost no influence upon measures directed to combat the disease, which have remained practically unchanged since the era when knowledge of Koch's discovery of the tubercle bacillus became widely disseminated.

For at least two decades we have known that nature has somewhat inefficiently accomplished for tuberculosis that method of protective inoculation that has been the most successful means of combating infectious disease. Smallpox has been largely overcome and typhoid fever is demonstrably controllable by protective inoculation. We know very well that few children in the large cities of America and Europe escape inoculation with tuberculosis before they reach adult life. Anatomic demonstration of the scars of healed tuberculous lesions and observations made by testing children with tuberculin have furnished convincing evidence that the tubercle bacillus is so widely disseminated that few escape contact intimate enough to produce an appreciable tuberculous lesion. Nevertheless the protection afforded by this natural inoculation, although it modifies the course of disease resulting from a second infection, is obviously inadequate to prevent it, or to ensure a favorable outcome.

I shall enumerate some of the evidence that helps to explain the pathogenesis of the disease.

Tuberculosis in infancy and early childhood resembles that produced experimentally in susceptible animals, such as the guinea

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pig. A focus of infection is rapidly followed by tuberculosis of the lymph nodes situated in the direction of the lymph flow and the disease may progress with much greater rapidity in the lymph nodes than at the primary site of invasion. This relation does not exclude the possibility that the primary focus may occasionally be so small or retrogress so far that it becomes unrecognizable. Nevertheless Küss and later Ghon found a tuberculous focus in the lungs and lesion of the adjacent lymph nodes almost invariably associated. In only a small part of the children in this country, probably not exceeding 5 per cent, the primary site of invasion is the intestinal tract with secondary lesions in the mesenteric lymph nodes but in Great Britain approximately one-fourth of adults retain in the mesenteric lymph nodes scars of primary infection, acquired in childhood by way of the intestinal tract.

Pulmonary tuberculosis in adults has, however, little resemblance to tuberculosis produced by the usual inoculation of animals. It is a chronic disease that proceeds slowly, often with cavity formation but at the same time with a tendency to heal as indicated by the production of fibrous tissue. In sharp contrast with the tuberculosis of early childhood it long remains localized in the parenchyma of the lung and even though a whole lobe is implicated the lymph nodes at its hilum exhibit none of the characteristic changes of tuberculosis. This localization of the lesion at the site of invasion is reproduced in experimental animals only when an animal previously infected is reinfected with the tubercle bacillus. Koch found that a second infection, unlike the first, is followed by a prompt reaction, which tends to heal with no involvement of the nearest lymph nodes.

Renewed study of the anatomic pathology of tuberculosis has in very recent years extended our knowledge of the disease. Roentgenologic films prepared from lungs removed after death are an effective aid in the discovery of the calcified scars of healed tuberculosis acquired during childhood.[1] By this means, we seldom fail to obtain proof that those who die from the chronic pulmonary tuberculosis usual in adults have sustained an earlier infection. The characters of this form of the disease are not determined by changes in the lungs peculiar to increasing age but are the result of the increased resistance conferred by a first infection, as is shown by the now abundant evidence proving that pulmonary tuberculosis in a person who has escaped infection during childhood has all the characters of infantile tuberculosis. It extends rapidly in the lungs, implicates the adjacent lymph nodes and brings about massive caseous enlargement of them. Death often occurs, as it does in young children, from disseminated miliary tuberculosis. In such instances, occurring usually in colored adults, scars of existing infection cannot be found even when Roentgen ray films are used to aid the search.

Should the attempt be made to determine the significance of the

widespread prevalence of minor infections with tuberculosis demonstrated by anatomic lesions in the bodies of those who die from causes other than tuberculosis and by the corresponding frequency with which children react to tuberculin, two questions have outstanding importance: (1) What are the nature and limitations of the immunity conferred by infection? (2) What correlation exists between sensitization to tuberculin and immunity against the disease?

Observations made upon small laboratory animals beginning with the studies of Koch, Trudeau and Römer and a mass of evidence derived from experiments on cattle with the bovovaccine of von Behring and other attenuated tubercle bacilli have shown that immunity against tuberculosis has several inconvenient features.

Resistance, though materially increased by a first infection, is readily overcome by increasing the reinfecting dose. This relation has been repeatedly demonstrated by varied experiments. Hamburger[2] even found that a small reinfecting dose injected into the skin on one side of a guinea pig produced a lesion that healed rapidly whereas a larger dose on the other side caused progressive tuberculosis.

Moreover such resistance as is conferred is transient and disappears after recovery from infection. Löwenstein has said, "Only the tuberculous animal is immune." Observations with the bovovaccine of von Behring, for example, showed that resistance usually disappeared after a few months and rarely persisted after one year.

The degree of resistance conferred by inoculation increases with the virulence of the microörganism used. From the standpoint of human protection this relation is conspicuously undesirable for the agent that gives the greatest resistance to reinfection is itself a grave source of danger. This consideration is responsible for the total abandonment of the effort to protect cattle from spontaneous infection by inoculation with human tubercle bacilli (bovovaccine of von Behring), for, as Theobald Smith and others showed, human tubercle bacilli may produce such advanced tuberculosis of the udder that tubercle bacilli appear in the milk.

Human pathology furnishes a significant illustration of the danger accompanying protective inoculation. The early tuberculous infections of childhood afford a certain degree of protection against reinfection and when it occurs profoundly modify its course, yet these childhood infections, as I shall show later, vary widely in intensity and even when long concealed or latent may ultimately cause active disease and death.

Efforts to protect by tubercle bacilli rendered harmless by destructive agents have had little success. Tubercle bacilli killed by heat produce some immunity against infection with the living microorganism but Trudeau found this resistance less than that which followed inoculation with an attenuated culture. Skin sensitization

after injection of the dead bacillus has been noted by some observers (for example, Baldwin) and denied by others. By repeated injection into the peritoneal cavity of guinea pigs Petroff and Stewart[3] were almost uniformly successful in producing strong sensitization, which persisted for many months. These animals exhibited some increased resistance to infection (Zinsser, Ward and Jennings[4]) for they lived about six weeks longer than infected controls (Petroff and Stewart).

Inoculation of human beings with bovine tubercle bacilli attenuated by long-continued growth on media containing bile (BCG) has been introduced by Calmette and Guérin[5] and is now widely practised. Their observations suggested that the immunity produced by it differs from that heretofore associated with experimental tuberculosis for they maintained that their bacillus was totally lacking in virulence and produced no tubercles when injected into animals. Observations by R. Kraus[6] of Vienna and by Petroff, Branch and Steenkin[7] have, however, shown that massive doses (5 mg.) will occasionally cause death of guinea pigs and it is now well recognized that the virus produces typical tuberculous lesions at the site of injection, in adjacent lymph nodes and occasionally elsewhere. Fed to infants by mouth as recommended by Calmette it seems to be harmless, but its efficacy when thus administered may still be questioned. There has been wide difference of opinion concerning the immunity that BCG produces in experimental animals.

Calmette has used the BCG virus to protect infants in contact with tuberculosis and has recommended its administration by mouth during the first ten days of life. The statistical evidence collected in this splendid endeavor indicates that the virus has some value but the validity of these statistics is in dispute. Protective inoculation would presumably have little value in children in whom a skin reaction to tuberculin showed that spontaneous infection had already occurred, for the virulent human bacillus would doubtless have already afforded a more effective protection. Furthermore protective inoculation at best evidently furnishes uncertain resistance against subsequent infection, for many children in whom tuberculosis of tracheobronchial lymph nodes is recognizable by roentgenologic examination of the chest, acquire apical tuberculosis if their contact with open tuberculosis is continued during adolescence.

There is no adequate understanding of the nature of the limited *immunity* of the tuberculous animal against reinfection. Agglutinin and complement fixing and bacteriotropic antibodies make their appearance in the blood serum but it has not been possible to determine exactly what part they play in the destruction of tubercle bacilli. Nevertheless it is highly probable that these bodies, notably bacteriotropic substances promoting the phagocytosis that is so

conspicuous during the progress of the disease, are essential factors in the struggle against the microörganism. Knowledge of the subject is astonishingly incomplete.

One phenomenon of immunity against tuberculosis and many other infections deserves, I believe, more consideration than it has received, namely, the heightened capacity of the reinfected animal to form antibodies. The first observations demonstrating that an animal once immunized forms antibodies more rapidly than a normal animal were made by Cole[8] studying agglutinins for the typhoid bacillus. Mudd, Lucké, McCutcheon and Strumia[9] in our laboratories have shown that animals when infected a second time form bacteriotropic antibodies, agglutinins and a substance promoting the wetting of tubercle bacilli much more rapidly after a second than after a first infection. It is desirable to learn whether the animal that has apparently lost its immunity after complete recovery from tuberculous infection still retains this power to immunize itself more rapidly than an animal previously uninfected.

One of the most puzzling phases of the pathogenesis of tuberculosis is the apparent paradox of hypersensitiveness and immunity. I shall avoid the term allergy because although it was introduced in order to include immunity it is used almost exclusively as a synonym for hypersensitiveness. Since hypersensitiveness is in great part at least the heightened capacity of the tissues to react with acute inflammation I shall discuss inflammatory reactions produced by the tubercle bacillus.

Much confusion has resulted from the attempt to define the relation of inflammation to tuberculosis. It is universally recognized by those who have directed their attention to the matter that tubercle bacilli when first introduced into the body produce all of the early phenomena of inflammation, with exudation of plasma, deposit of film and accumulation of polynuclear leukocytes. This phase of the reaction is transient and usually inconspicuous in comparison with the accumulation of mononuclear cells that follows. Information concerning the chemical constituent of the tubercle bacillus responsible for this reaction is no more accurate than that applicable to other microörganisms.

I shall not renew in detail discussion concerning the domain of inflammation in relation to tuberculosis. As with inflammation caused by other bacteria, accumulation of mononuclear cells is an essential part of the process. Use of the term "exudative" applied to accumulation of serum fibrin and polynuclear leukocytes and "proliferative" applied to the assembling of mononuclear cells has little to support it. Proliferation of the fixed tissue of the part becomes evident when collagen fibers are formed and is represented in its earliest stage by the reticular fibers of tuberculous tissue accurately described by Miller.

The accentuation of the early phases of inflammation character-

ized by redness, swelling and the accumulation of polynuclear leukocytes that occur with reinfection of a tuberculous animal was early recognized by the discovery of the tubercle bacillus and is an essential part of "Koch's phenomenon." It soon became evident to him that similar changes were produced by separable products of the tubercle bacillus. The tuberculin reaction is an acute inflammatory reaction, which when sufficiently intense proceeds to necrosis. Tuberculin (OT) or a water extract of tubercle bacilli introduced into the dermis of a normal guinea pig causes an inconspicuous inflammatory reaction with exudation of many polynuclear leukocytes still recognizable forty-eight hours after injection. The intense inflammatory reaction that occurs in a tuberculous animal is an accentuation of this process and does not differ essentially from it. Mononuclear cells assemble at the periphery of the lesion where the action of the irritant is least severe and gradually encroaching upon the polynuclear leukocytes ultimately replace them.

The changes at the site of reinfection with tubercle bacilli are the same in character. Jaffe and Löwenstein,[10] Krause[11] and others have described the acute inflammatory reaction that occurs when the skin is the site of reinfection. Rapid accumulation of polynuclear leukocytes aid in the separation of necrotic tissue, superficial ulceration occurs and healing with new formation of fibrous tissue follows.

Changes that occur at the site of reinfection with tubercle bacilli resemble very closely those that occur in animals sensitized to foreign protein. Anaphylactic inflammation, or the Arthus phenomenon, occurs in animals, such as the rabbit, after repeated injections with a foreign protein like horse serum or egg white.[12] When the foreign protein is first injected into the skin of a normal animal it rapidly leaves the site of injection, produces no inflammatory reaction and enters the circulating blood, where it remains until antibodies, for example, precipitin, make their appearance. In the animal that has been immunized (and sensitized) reinjection with the foreign protein produces an intense inflammatory reaction with necrosis at the site of entry. I have shown that the foreign protein is arrested by the inflammatory reaction at the site of injection, from which it may be recovered almost quantitatively, and so fails to enter the circulating blood. The paradox between susceptibility to local inflammation and necrosis on the one hand and resistance, that is, immunity, on the other is only apparent, for the local inflammatory reaction is an effective means for the protection of internal organs.

Incidentally it is noteworthy that hypersusceptibility to foreign protein is referable to an antibody recognizable in the blood serum of the sensitized animal, for it can be passively transferred to a normal animal by injecting serum of one that is sensitized. Varied experiments have shown that whenever the antigen and this anti-

body are brought together in the tissues of a normal or immune animal, anaphylactic inflammation follows. The analogy between sensitization with foreign protein and the hypersusceptibility of the tuberculous animal to tuberculin is not complete for in the latter the intervention of an antibody, as shown by passive sensitization, has not been demonstrated satisfactorily. Nevertheless the analogy is supported from another point of view for the animal sensitized by tuberculous infection has the ability not possessed by a normal animal to fix tubercle bacilli at their site of entry.

Krause and Willis[13] have recently demonstrated by inoculation of excised tissue into guinea pigs that there is in normal guinea pigs rapid dissemination of tubercle bacilli from the site of inoculation, whereas in animals previously infected dissemination is retarded. Transit of the bacillus from the point of entry in the skin to the axillary or inguinal lymph nodes, 4 or 5 cm. distant, was made in twenty-four hours or less but in animals rendered resistant by previous infection passage to the lymph nodes required two or three weeks. In the immunized animal some of the bacilli introduced into the skin ultimately reach distant parts of the body, but their number is relatively small.

Since acute inflammation is the immediate result of reinfection it is pertinent to inquire whether this reaction retards the dissemination of bacteria. A series of experiments recently performed with hemolytic streptococci has shown that inflammation of the peritoneal cavity caused by a sterile irritant, namely, aleuronat, in the early stages retards and after twenty-four or forty-eight hours completely prevents the rush of bacteria into the blood stream that invariably follows introduction of streptococci into the peritoneal cavity of a normal animal.

I have emphasized the foregoing relationship because with human tuberculosis inhibition of dissemination is one of the most conspicuous features of the disease in adults who have sustained the usual infection of childhood. In infancy and early childhood a focus of infection in the lung or intestine is immediately followed by tuberculosis of the regional lymph nodes and the lesion of the lymph nodes in most instances becomes much larger than the original focus. When the disease progresses, usually as the result of massive infection, death occurs from general dissemination of tubercle bacilli by way of the blood stream. Tuberculosis of the adult occurs with few exceptions in the lung and here first affects the apex. This lesion long remains localized in the apex and even when it spreads by way of the bronchial tree is limited to the lung. In contrast with the tuberculosis of infancy and early childhood pulmonary tuberculosis of adult type fails to implicate the nearest lymph nodes even when it is scattered over a whole lung. Some dissemination may occur in the terminal stages of fatal pulmonary tuberculosis of adults but miliary tuberculosis is rarely if ever seen.

Among school children of Philadelphia 54 per cent between the ages of five and nine years react to tuberculin; 76 per cent between ten and fourteen and 83 per cent from fifteen to nineteen years. In what degree can the reaction be used as evidence of immunity against tuberculosis? Both experimental and clinical evidences show that accompanying resistance is uncertain in the event of massive infection. Some writers have assumed that local susceptibility to tuberculin indicates hypersusceptibility to tuberculosis and Ranke,[14] who assumed the occurrence of a primary, secondary and tertiary stage of tuberculosis analagous to the conventional stages of syphilis defined them as: (1) a stage of invasion; (2) a stage of hypersusceptibility with dissemination of lesions, and (3) a stage of chronic pulmonary tuberculosis with immunity. I have already assembled evidence that, I believe, is incompatible with this view; hypersusceptibility does not precede immunity but the two proceed hand in hand. Experimental evidence, as I have pointed out, indicates that the inflammatory reaction that tuberculin produces in a susceptible animal prevents dissemination of bacteria.

Nevertheless this reaction that is elicited by products of the tubercle bacillus even after they have undergone profound alteration, does not necessarily bring about destruction of the microörganism. It is well known that the reaction makes its appearance about the time when antibodies become demonstrable in the blood but is apparently well established before resistance has reached a maximum. Observations upon cattle made with the bovovaccine of von Behring furnish suggestive evidence that immunity is not necessarily accompanied by hypersusceptibility to tuberculin (Strelinger). The tuberculin reaction is conclusive evidence of tuberculous infection and the evidence at hand shows that it is inseparably associated with the phenomena of immunity. Its presence, like the otherwise dissimilar skin tests of diphtheria and scarlet fever, implies some immunity against infection but as yet it cannot be used as a measure of the degree of resistance.

Studies made by Lurie[15] at the Henry Phipps Institute give very intimate information concerning the relation of the tubercle bacillus to the pathogenesis of the disease and help to explain why the lung suffers more severely than other organs, even when resistance is increased by preceding infection. He has followed the fate of tubercle bacilli in the lungs, liver, spleen, kidney and bone marrow of rabbits injected intravenously by both human and bovine tubercle bacilli and at varying intervals during the course of the infection has estimated the number of surviving bacteria by a method that enables him to count the number of colonies obtainable on suitable media from a weighed quantity of each organ. Tubercle bacilli, like other particulate matter injected into the blood stream, are deposited in greatest abundance in the spleen and in other organs in diminishing number in the order of liver, lung, bone marrow and

kidney. At first tubercle bacilli multiply in all of the organs, the human bacillus, in agreement with its behavior *in vitro*, more rapidly than the bovine. With the bovine type destruction of tubercle bacilli begins after four weeks in the liver, spleen and bone marrow and continues uninterruptedly, although the microörganism multiplies in the lung and to less extent in the kidney, until death ensues. With the human bacillus multiplication in the lung is far greater than in other organs and destruction here proceeds more slowly than elsewhere but in all of the tissues examined destruction begins between the second and fourth week and proceeds rapidly as the animal recovers. In rabbits reinfected with both human and bovine strains of tubercle bacilli there is no preliminary multiplication in any of the organs and destruction in liver, spleen and bone marrow follows inoculation immediately. Nevertheless even though the animals resist infection tubercle bacilli persist in the lungs in large number. It is noteworthy that a few tubercle bacilli survive for months in all of the organs of reinfected animals even though they exhibit no anatomic evidence of tuberculosis.

Knowledge of the widespread dissemination of tuberculous infection and the occurrence of reinfection suggest many new problems concerning the transmission of the disease. How are these latent infections acquired? Under what conditions does reinfection occur?

Experimental transmission by contact rather than by inoculation is a method of study that has not received the attention it deserves. The difficulties of investigating the spread of a disease that develops slowly during weeks or months are very great but can be overcome. The only systematic study of the experimental epidemiology of tuberculosis has been made by Perla[16] at the Henry Phipps Institute. A large part of those who are engaged in the experimental study of tuberculosis believe that spontaneous tuberculosis of guinea pigs occurs seldom if at all, but as Koch recognized many years ago, it is a possible source of error in all experiments in which these animals are kept together in considerable number after they are infected with tuberculosis. When normal guinea pigs were kept in cages with others infected by way of the peritoneal cavity and with no superficial ulceration from 22 to 60 per cent acquired tuberculosis after seven months, the number varying with crowding and other conditions. Perla found that infected animals, in the latter period of the disease, eliminated tubercle bacilli with the feces and normal animals are infected by way of the gastrointestinal tract with secondary involvement of the mesenteric lymph nodes. Dr. Lurie has continued these experiments and has found that vaccinated animals resist infection. The method of study, though laborious, promises to aid the solution of important questions concerning the transmission of tuberculosis.

At the present time the epidemiology of human tuberculosis can be studied more satisfactorily than that of animals. In the past this

study has been pursued in large part by statistical methods with disappointing result for there is today nearly as much uncertainty concerning the contagion of phthisis as there was centuries ago.

Until the last few years nothing has been known concerning the distribution and severity of tuberculous infection among those who give no evidence of the disease and are presumably in good health. We have been wholly ignorant of the relation of latent infections to clinically manifest disease and of the conditions under which latent infection becomes manifest disease.

It is evident that no accurate knowledge of the epidemiology of tuberculosis is obtainable as long as these latent infections are ignored. As little could be learned concerning the epidemiology of influenza if it were arbitrarily agreed that attention should be limited to those who developed pneumonia.

Study of the pathologic anatomy of latent tuberculous infection has directed my attention to the need of accurate knowledge concerning its occurrence during life and its mode of spread. Two means are available for the discovery of lesions unaccompanied by significant symptoms or physical signs, namely, the tuberculin reaction and roentgenologic examination. Roentgenologic examination of the chest, successfully performed only when many obstacles are overcome, is an effective and often exact method of depicting the extent of anatomic changes caused by tuberculous infection. Unfortunately it does not reveal some of the earliest changes.

During the last five years the dispensary of the Henry Phipps Institute has been organized to assemble by its routine operation information concerning the occurrence of latent as well as clinically manifest tuberculosis, to trace the spread of infection by contagion within the household and elsewhere and finally to determine by observations continued over a period of years under what conditions latent develops into manifest disease. This endeavor has been in large part successful and has evolved a dispensary system that, from a wholly practical standpoint, is an effective means for the prevention of tuberculosis.

The essential features of the procedure are as follows:

Search for latent as well as manifest tuberculosis and the attempt to determine whether it is sufficiently advanced to menace health.

Routine application of the intradermic tuberculin test interpreted in relation to the age and to the character of the associated lesions.

Roentgenologic chest examinations directed to determine the position and extent of latent and clinically manifest lesions and repeated often enough to reveal the progress of the disease.

Social service by a nursing staff trained to give care to patients and their families and to collect information not obtainable from the patient.

The preparation of a graph that pictures the origin and progress of tuberculosis both manifest and latent within the household.

Investigation of the family as a unit of infection, and prophylactic care guided by all the information that has been assembled.

A study of the spread of tuberculosis in families has been undertaken by Dr. McPhedran and the author.[17] The usual method of sputum examination, if repeated often enough, is an accurate measure of the danger to which a household is exposed. In families in which some member suffered with tuberculosis and expelled tubercle bacilli with the sputum, the incidence of latent tuberculosis, as indicated by the tuberculin test, was very high; 80 per cent of children of contact families react to tuberculin before they reach their fifth year of life, whereas at the same age less than 30 per cent of children are sensitive to tuberculin.

Furthermore roentgenologic examination revealed latent or manifest tuberculous lesions four times as frequently in contact as in noncontact families and showed that the lesions in contact families were far more severe in character and extent. Latent tuberculosis of the tracheobronchial lymph nodes occurred seven times as often in contact as in noncontact families. Approximately 1 in 10 of the children exposed to open tuberculosis had acquired manifest tuberculosis before they had reached adult life.

This study conducted during a period of five years has demonstrated for the first time how frequently advanced latent lesions develop into manifest disease. The recognition of advanced latent tuberculosis furnishes a means by which the onset of tuberculosis may be predicted within certain limits years even before it has begun to undermine health. These observations have demonstrated the value of repeated roentgenologic examination of children exposed to tuberculosis and make it possible to forestall by appropriate prophylactic care the transition of advanced latent into manifest disease.

During early childhood two lesions, recognized by roentgenologic examination in combination with the tuberculin test, are especially significant as precursors of manifest disease, namely, diffuse infiltration of the lung parenchyma identified as tuberculous and tuberculosis of tracheobronchial lymph nodes.

Infiltration of lung parenchyma occurring in young children and seldom situated in the apex is recognized by roentgenologic examination and is usually associated with a very active tuberculin reaction though unaccompanied by symptoms or physical signs of pulmonary disease. Tuberculosis of tracheobronchial lymph nodes is doubtless, as autopsies show, invariably associated with the lesion but moderately enlarged caseous lymph nodes are not recognizable unless they have undergone some calcification. Nevertheless tuberculosis of tracheobronchial lymph nodes, evident in Roentgen ray films, is associated with infiltration of the parenchyma in about half of all instances. The lesion of the lung parenchyma that remained latent during months or even years of observation may finally manifest

itself by cough, loss of weight, fever and physical signs over the affected area.

Tuberculosis of tracheobronchial lymph nodes evident by roentgenologic examination in more than one-fifth of children exposed to open tuberculosis seldom produces recognizable symptoms or physical signs but is in many instances the precursor of manifest disease of the lung. This in younger children has the character of the pulmonary infiltration just described and is due to progressive increase of the primary focus of infection, which was not visible when the tracheobronchial lesion was first recognized.

In adolescent children, however, the pulmonary lesion like that of adult life makes its appearance in the apex of the lung, bears no anatomic relation to the lesion of the bronchial lymph nodes as autopsies show and appears after this lesion has undergone calcification. When the two lesions occur in a child long in contact with open tuberculosis it is probable that apical tuberculosis is due to continued exposure to the source of infection responsible for the tracheobronchial lesion. The latter is evidence of exposure to open tuberculosis and protection from further infection may prevent manifest disease.

Mortality from tuberculosis reaches a high peak during the first year of life, falls rapidly during the second year and gradually diminishes during several subsequent years. From the fifth to the fifteenth year the death rate from the disease is lower than at any other time of life. From the twelfth year to the fifteenth year in girls and somewhat later in boys, the death rate from tuberculosis begins to rise and reaches a maximum in early adult life. Tuberculous infection in the period between the fifth and fifteenth years has the characters of the disease of childhood and it tends to pursue a benign course. In adolescence the adult apical type makes its appearance and the death rate from tuberculosis begins to increase.

Roentgenologic studies at the Henry Phipps Institute have revealed the frequency with which apical lesions occur in adolescent children of families exposed to open tuberculosis. These children are often in excellent health and just as often over- as underweight. Apical lesions may pursue a benign course but not infrequently after a few months, or more frequently after several years, the characteristic symptoms and physical signs of pulmonary tuberculosis ensue. We have repeatedly followed its course from the appearance of a small shadow below the margin of the second rib with no other evidence of disease, during a period of gradual extension of the lesion, until active disease is manifested by symptoms, physical signs and tubercle bacilli in the sputum. Years ago Newsholme pointed out the long latent period between exposure to infection and the onset of phthisis. The latent apical lesions of adolescence are precursors of a large part of the phthisis of early adult life. Recognition of these latent lesions and the application of well-established

procedures to prevent further extension of tuberculous infection promise to become important factors in the control of the disease.

The opinion upheld by von Behring and many others that all tuberculosis is acquired in early childhood still has many supporters. The strongest evidence in favor of the view that adults do not acquire the disease is derived from statistics that show the incidence of the disease among husbands or wives of consumptives. Vast figures representing the histories of over 50,000 persons who have been exposed to marital infection have failed to give decisive information concerning adult infection.[18] The accuracy of the mathematical methods of Pope and Pearson and others who have investigated the problem can scarcely be doubted but the value of the data they have used is at least questionable. Direct observations continued during a period of years with the aid of roentgenologic examination, which on the one hand is an effective aid to the diagnosis of manifest tuberculosis and on the other hand discloses tuberculous infection unaccompanied by symptoms or physical signs, give more trustworthy information. In a small group of families in which husband or wife suffered with open tuberculosis we found evidence that the infection had been transferred to the consort in nearly half of those whom it was possible to examine. Subsequent observations continued during the last five years have amply confirmed this observation. Both manifest and latent tuberculosis is far more common in the consorts of persons suffering with open tuberculosis than in those not exposed to marital infection.

Infection from without during adult life can scarcely be doubted. Nevertheless endogenous infection from a preëxisting lesion cannot be denied; indeed it is probable that in a person who has become resistant as the result of existing infection endogenous and exogenous infection would have similar results. All of the evidence that is available indicates that the pulmonary tuberculosis of adults is acquired with few exceptions from without. This is certainly true of the marital infection just described. Anatomic evidence proves that the apical tuberculosis of adults is not the result of extension from the focal lesions of first infection for the two are usually separated widely and as often in opposite as in the same lungs. Study of the bacteriology of focal nodules of first infection in the lungs and bronchial lymph nodes, made by Dr. Aronson and the author,[19] show that tubercle bacilli have disappeared when encapsulation begins so that the lesions of first infection are free from tubercle bacilli at a time when the apical lesion of adult type makes its appearance.

Webb[20] objects to this conception of the pathogenesis of tuberculosis because he says we know no other parasite that must twice infect the same host in order to complete its life history. Two infections of the host are, however, not essential, for the lesion of first infection by caseation into a bronchus might transmit the disease and this was doubtless the primitive mode of transmission.

Theobald Smith has suggested that the tubercle bacillus tends to adapt its virulence to the resistance of its host so that it may produce a long-continued disease favorable to its dissemination. With widespread latent infection virulence might be modified to produce long-continued disease in a partially immunized host.

A survey of tuberculosis among children in the public schools of Philadelphia made by Dr. Hetherington, Dr. McPhedran, Dr. Landis and the author during the last three years has extended our knowledge of the epidemiology of the disease and revealed the frequency with which infection varying in character and extent occurs in children who are presumably healthy. One purpose of the survey has been to determine what children have such grave infections that they require care in the open-air schools now maintained by almost all of the large cities of this country. It is noteworthy that the system of medical inspection of schools in Philadelphia is highly efficient and excludes from the school tuberculosis recognizable by the usual procedures. All of those who have given attention to the matter admit that the usual methods of physical diagnosis discover tuberculosis only after it is far advanced and can be benefited if at all only by sanatorium treatment or its equivalent. Loss of weight, as Hetherington[21] has shown, is a late manifestation of tuberculosis and cannot be used as a criterion of grave latent infection. By tuberculin tests, roentgenologic films and physical examination, we have sought to find the various types of latent infection discussed in this lecture.

The results of tuberculin tests made by the intradermic method upon 4100 children suggest some conclusions of general interest. Classified in accordance with age they show that the incidence of the reaction increases from 47.2 per cent at the age of five years to 95.3 per cent at eighteen. They furnish no support to the opinion that the prevalence of concealed infection has diminished parallel with the diminishing mortality from tuberculosis in recent years. Our figures do not differ materially from those collected by Hamburger and Monti twenty years ago in one of the most crowded cities of Europe, namely, Vienna. Furthermore, not only is latent tuberculosis so widespread that few children escape before they reach adult life but in many instances it is so advanced that it is a grave menace to life. The astonishing prevalence of these advanced infections suggests that mortality from tuberculosis will promptly increase if conditions favorable to the disease should reappear.

Our survey has shown that 0.5 per cent of the school children we examined have manifest tuberculosis recognizable by physical examination and roentgenologic films. Latent tuberculous infiltration of the lungs of the type of childhood was found in 2 per cent of children and was evidently more significant in younger children. Latent apical tuberculosis (adult type) was found in 1 per cent of

children, in large part in high-school pupils between the ages of fifteen and eighteen years.

Both sex and race modify the frequency and severity of tuberculous infection in school children.

Minor infections indicated by tuberculin tests and calcified nodules in lungs and lymph nodes are somewhat more frequent in girls than in boys but the graver latent infections, revealed by infiltration of the lung parenchyma and especially by latent apical infection, are much more frequently found in girls than in boys. Particularly significant is the high incidence of clinically manifest tuberculosis in adolescent girls. Of boys of high-school age only 0.4 per cent had clinically recognizable tuberculosis whereas of girls 1 per cent were affected.

We have found minor tuberculous infection less frequent in colored than in white children but graver infections and especially clinically manifest disease are found much oftener in colored than in white children. Manifest tuberculosis was found in 0.6 per cent of white children between twelve and eighteen years of age and in 2.4 per cent of colored children of the same ages. Protective infection seems to occur less frequently in the colored than in the white and when colored children are infected with tuberculosis, especially during adolescence and early adult life, grave disease is more likely to ensue.

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REVIEWS.

RICKETS, INCLUDING OSTEOMALACIA AND TETANY. By ALFRED F. HESS, M.D., Clinical Professor of Pediatrics, University and Bellevue Hospital Medical College, New York City. Pp. 485; 52 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $5.50.

SINCE the publication of Dick's book in 1922, an immense amount has been written on the subject of rickets. The realization of its widespread prevalence and the invasion of its field advertising copy have aroused an enthusiasm in research unsurpassed by any field of modern medicine.

Beyond doubt the one most fitted for such a duty, Hess has collected the researches of workers the world over, has scanned their results and evaluated their conclusions in this book, which, be it clearly understood, is a monograph and not a handbook.

Separate chapters are devoted to etiology, pathogenesis, pathology symptomatology, diagnosis and treatment. Each is discussed fully and a bibliography appended. The matter of the metabolism is considered separately and there is a splendidly illustrated chapter on the radiographic changes of rickets.

The chapter on treatment is gratifying complete and of special interest because of the recent questioning of the harmlessness of irradiated ergosterol. The author's endorsement of it, his recommendations as to dosage and his precautions as to its use, should be known to every pediatrist.

The Reviewer feels that this was a much needed book and that in it the need has been most admirably filled. It should be in the possession of every pediatrist and student of metabolic diseases.

J. S.

SURGICAL DISEASES OF THE THYROID GLAND. By E. M. EBERTS, M.D., Surgeon to the Montreal General Hospital, Associate Professor of Surgery, McGill University, with the assistance of R. R. FITZGERALD, M.D., and PHILIP G. SILVER, M.D. Pp. 238; 48 engravings. Philadelphia: Lea & Febiger, 1929. Cloth, Price, $3.50.

IN the preparation of this volume, the authors have drawn largely upon their personal experience at the Goiter Clinic of the Montreal General Hospital. They have clearly and concisely presented

practically all that is known and much that is theory concerning the thyroid gland and its diseases.

The first part of the book is given over to a consideration of the embryology, anatomy, physiology and pathology. The second part discusses the clinical side of the various forms of goiter. Except for a few suggestions, very little space is given to the operative technique, but the chapters on preoperative and postoperative treatment are excellent. Throughout the clinical part of the book, case reports are used to illustrate the text, perhaps in too great profusion. At the end of many chapters is given a short bibliography.

The monograph is well written, and is highly recommended to those who are interested in the diagnosis and treatment of thyroid diseases. L. F.

A System of Bacteriology in Relation to Medicine. By Various Authors. Vol. III. Economic Bacteriology, Plague, Anaërobes, Food Poisoning. Pp. 413; 13 illustrations. London: His Majesty's Stationery Office, for the Medical Research Council, 1929. Obtainable in the United States at British Library of Information, 5 East 45th St., New York. Price, £1.1.9, for this volume; for the set, £8.14.9.

An authoritative and adequate System of Bacteriology in English is indeed a boon to contemporary medical science. Those who have sufficient German are so used to turning to German sources and those without German to doing without this aid to investigation that it will be an especially pleasant change to have this source of information in our own language. The British National Research Council has therefore again put the medical profession in its debt by fostering this monumental undertaking. With the unavoidable constant increase in medical specialization, such works become increasingly necessary in facilitating acquisition of information in a perhaps closely related but little known field. As Lord Balfour, Chairman of the Medical Research Council, says in the General Preface, "No investigator, however narrow may be his intensive study of one aspect of one problem, need henceforth feel that in cultivating this small part he must lose his vision of the whole; and no one endeavoring to the best of his ability to form some general picture of the whole need doubt that with the aid of this System of Bacteriology he will succeed in his efforts."

This third volume—the first published—deals with such topics as the Economic Aspects of Bacteriology (Thaysen); the Bacteriology of Water (Henry); of the Dairy Industry (Vollum); of Foods (Savage); of the Soil (Thornton); Bacterial Diseases of Insects (St. John-Brooks); of Plants (Paine); Gas Gangrene (Robertson and O'Brien); Bacillus Pestis (Petrie and Bulloch); Bacillus Tetani (Fildes and

others); Bacillus Botulinus (Hewlett and others) and Bacterial Food Poisoning (Savage).

It is beyond the scope of this review or the ability of the Reviewer to evaluate these chapters in detail, but many of the names should carry sufficient conviction in themselves. A further recommendation in these days of reckless bookmaking and charging is the very modest price—a guinea for a volume of this kind, or less than 9 pounds for the set of 9 volumes, is a refreshing relief from the prices charged in Germany especially and to a lesser extent in this country. Let us hope in the interests of science that it will have a correspondingly wide sale. E. K.

A SYSTEM OF BACTERIOLOGY IN RELATION TO MEDICINE. VOL. IV. THE ENTERIC GROUP, VIBRIOS, PASTEURELLA. By VARIOUS AUTHORS. Pp. 482. London: His Majesty's Stationery Office for the Medical Research Council, 1929. Obtainable in the United States at British Library of Information, 5 East 45th St., New York. Price, £1.1.9 for this volume; for the set, £8.14.9.

THE chapter of 85 pages on "Bacillus Typhosus" is apparently written mostly by D. Harvey, though designation of the parts written by the associated authors is not clearly made. The introductory historical section seems inadequate; Bretonneau's contribution is overemphasized, Gerhard's entirely omitted. On page 35 it is stated that the hematohepatogenous route of infection is probably the usual one in man, yet on page 39 the more conventional route of passage through the intestinal wall of the lymph spaces, nodes and spleen is supported. More than half of the 167 references are to British sources, an imbalance probably due to greater familiarity with the native literature than to conscious chauvinism. Perhaps for the same reason, the American literature seems to the Reviewer specially to have been neglected in spots. Much space is properly devoted to serologic reactions and immunization. Dreyer's quantitative agglutination estimation—the important British contribution to this phase—is mentioned but will be described in Vol. IX. The invaluable immunization experiences of the war are emphasized, though Leishman's earlier work and that of Russell in the American Army mostly or entirely omitted from consideration. It is not meant to imply, however, that such shortcomings detract materially from the value of the presentation as a whole.

While space forbids a similar discussion of the other chapters on the Salmonella Group, Dysentery, Colon Groups, Cholera Vibrio, Pasteurella Trevisan and Bacillus Pseudotuberculosis Rodentium, it can safely be asserted that they are valuable contributions to the subject. The lack of uniformity in presenting references—some at end of chapters, others at end of sections—is a minor regrettable item. E. K.

INTERN'S HANDBOOK. By Members of the Faculty of the College of Medicine, Syracuse University, under the direction of M. S. DOOLEY, A.B., M.D., Chairman, Publication Committee. Pp. 236. Philadelphia: J. B. Lippincott Company, 1929. Price, $3.00.

THIS little book should be of inestimable value to every intern. It presents in small space a wonderful amount of important knowledge that otherwise must be obtained from one of a dozen textbooks. Much useful information is given on drugs, their action, costs, advantages, and so forth, together with a pharmacy list. Standard clinical procedures, medical, surgical and special dietaries, techniques and routine lists, all are clearly and succinctly presented. Instructions as to the conduct of action in emergencies is given clearly and in detail.

The book is a "find" for any intern. B. E.

DISEASES AND DEFORMITIES OF THE SPINE AND THORAX. By ARTHUR STEINDLER. Pp. 573; 76 illustrations. St. Louis: C. V. Mosby Company, 1929. Price, $12.50.

DOCTOR STEINDLER has added another valuable monograph to the literature of orthopedics.

The case matter presented is excellent and is apparently entirely from the author's clinic. The opinions expressed are entirely personal and although they may not meet with general agreement they are so firmly founded upon fact and experience as to demand most careful consideration.

The illustrations are many and excellent. The assembly of the material in outline form adds greatly to the ease of reference and assures logical sequence of substance. While the inclusion of basic facts and experimental data makes of this book an authoritative treatise which is highly recommended to both general practitioner and orthopedic surgeon. G. W.

SURGICAL AND MEDICAL GYNECOLOGIC TECHNIC. By THOMAS H. CHERRY, M.D., Professor of Gynecology, New York Post-Graduate Medical School and Hospital. Pp. 678; 558 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, $8.00.

ANY author who has sufficient energy to illustrate his own work after writing the text deserves critical praise. Cherry has profusely illustrated the operations discussed, some of the drawings being

really creditable while others are very inferior, many being repeated several times. The book is essentially a treatise on the author's methods and experience and contains no bibliography. The inclusion of hernia, intestinal operations and obstetrical procedures and the arrangement of the illustrations make the book unduly large. In the section on medical treatment the author enthuses over the value of diathermy. More careful editing could eliminate such spelling as "*fascia endoplevina*," MacKenrodt, procidenture and vulva outlet. With no desire to be unfair or hypercritical, the Reviewer regards the work as just another book. F. B.

THE HISTORY OF HEMOSTASIS. By SAMUEL CLARK HARVEY, M.D., Professor of Surgery, Yale University, Surgeon in Chief, New Haven Hospital. Pp. 128; 19 illustrations. New York: Paul B. Hoeber, Inc., 1929. Price, $1.50.

BLEEDING, even as early as broken bones, must have aroused the therapeutic skill of our prehistoric ancestors. Hemostasis, then, should have a history coeval with surgery and even today its known beginnings can be traced to the earliest civilizations. The present book—one of Hoeber's attractive historico-biographical series—deals chiefly with the cautery, the ligature and the tourniquet, though Lister and his scientific study of various ligatures, the effect of infections and so on, receive adequate and sympathetic consideration. Just as in the larger subject it is interesting to see how knowledge that had been painfully won through centuries was lost perhaps for centuries again, only to be relearned with more travail.

E. K.

GONORRHEA AND KINDRED AFFECTIONS IN THE MALE AND IN THE FEMALE. By GEORGE R. LIVERMORE, M.D., F.A.C.S., Professor of Urology, Medical Department, University of Tennessee; and EDWARD A. SCHUMANN, A.B., M.D., F.A.C.S., Associate Professor of Obstetrics, University of Pennsylvania. Pp. 245; 66 illustrations. New York: D. Appleton & Co., 1929. Price, $5.00.

THIS book represents the earnest efforts of two exceptionally capable men to break into a hard field; one where so little is new and so much is personal opinion and experience. They have been successful in presenting the subject devoid of radicalism and divested of the advocacy of any current therapeutic fad. Its conservatism is its best factor.

The first 127 pages cover acute, chronic and metastatic gonorrhea in the male. The preface promises "great attention" to pathology that is scantily borne out and wretchedly presented in 28 lines.

The authors preach gentleness in treatment but advocate drugs, in practice that some might call heroic, until one wonders if the pessimism voiced under prognosis is not the just results of the treatment used.

The remaining 131 pages devoted to the problem in the female are easy, concise reading and admirably presented. Its optimism is in contrast to the pessimism of the fore part, and one catches a glimpse of the gynecological viewpoint which recognizes the disease self-limited, while in the male (with its simpler problem) too many are still striving for the sterilisans magna, and believe that they, with their drugs, cure gonorrhea. A. R.

BOOKS RECEIVED.

NEW BOOKS.

*De Oculis.** By BENEVENUTUS GRASSUS. Translated by CASEY A. WOOD, M.D., LL.D. Pp. 101; 5 illustrations. California: Stanford University Press, 1929. Price, $5.00.

*Common Infections of the Female Urethra and Cervix.** By FRANK KIDD, M.A., M.CH. (CANTAB.), F.R.C.S. (ENG.) and A. MALCOLM A. SIMPSON, B.A., M.B., D.P.H. (CANTAB.). Pp. 197; 14 illustrations. New York: Oxford University Press, American Branch, 1929.

*Human Helminthology.** By ERNEST CARROLL FAUST, PH.D. Pp. 616; 297 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $8.00.

*Laboratory Methods of the United States Army.** EDITED BY CHARLES F. CRAIG, M.A., M.D. Pp. 696; 9 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $3.50.

A System of Bacteriology in Relation to Medicine.† By Various Authors. Vol. III. Pp. 413; 13 illustrations. London: His Majesty's Stationery Office for the Medical Research Council, 1929. Obtainable in the United States at British Library of Information, 5 East 45th St., New York. Price, £1.1.9 for this volume; for the set, £8.14.9.

A System of Bacteriology in Relation to Medicine.† By Various Authors. Vol. IV. Pp. 482. London: His Majesty's Stationery Office for the Medical Research Council, 1929. Obtainable in the United States at British Library of Information, 5 East 45th St., New York. Price, £1.1.9 for this volume; for the set, £8.14.9.

Oxford Monographs on Diagnosis and Treatment. EDITED BY HENRY A. CHRISTIAN, M.D., Sc.D., LL.D., Vol. V. *The Diagnosis and Treatment of Chronic Diseases of the Respiratory Tract.** By ELMER H. FUNK, M.D. Pp. 618; 182 illustrations. New York: Oxford University Press, American Branch, 1929.

Oxford Monographs on Diagnosis and Treatment. EDITED BY HENRY A. CHRISTIAN, M.D., Sc.D., LL.D., Vol. VI. *The Diagnosis and Treatment of Arthritis.** By RUSSELL L. CECIL, M.D., Sc.D. Pp. 216; 14 illustrations. New York: Oxford University Press, American Branch, 1929.

* Reviews of titles followed by an asterisk will appear in a later number.
† See this issue.

Surgical Clinics of North America (Philadelphia Number). Vol. IX, No. 5. Pp. 299; 111 illustrations. Philadelphia: W. B. Saunders Company, 1929. Price, paper $12.00; cloth, $16.00 per clinic year.

*Gastric and Duodenal Ulcer.** By ARTHUR F. HURST, M.A., M.D. (OXON), F.R.C.P., and MATTHEW J. STEWART, M.B. (GLASG.), F.R.C.P. Pp. 544; 159 illustrations. New York: Oxford University Press, American Branch, 1929. Price, $20.00.

*Hemorrhoids.** By CHARLES CONRAD MILLER, M.D. Pp. 124; 20 illustrations. Chicago: Modern Surgery Publications, 1929.

*Stone and Calculous Disease of the Urinary Organs.** By J. SWIFT JOLY, M.D. (DUB.), F.R.C.S. (ENG.). Pp. 568; 189 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $16.00.

*The Nervous System.** By E. E. HEWER, D.Sc. (LOND.) and G. M. SANDES, M.B., B.S. (LOND.), M.R.C.S., L.R.C.P. Pp. 104; 55 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $6.50.

*The Science of Nutrition Simplified.** By D. D. ROSEWARNE, M.R.C.S. (ENG.), L.R.C.P. (LOND.). Pp. 314; 7 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $3.50.

NEW EDITIONS.

*Modern Methods of Treatment.** By LOGAN CLENDENING, M.D. With Chapters on Special Subjects by Various Collaborators. Third edition. Pp. 815; 95 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $10.00.

*The Blood Picture.** By PROF. DR. VICTOR SCHILLING. Translated and Edited by R. B. H. GRADWOHL, M.D. Seventh and eighth revised edition. Pp. 408; 48 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $10.00.

Memoranda of Toxicology. By MAX TRUMPER, B.S., A.M., PH.D. Second edition. Pp. 214. Philadelphia: P. Blakiston's Son & Co., Inc.

A convenient booklet for emergencies, with compact information easily available. Recent developments, such as barium, tetra-ethyl lead, methyl chloride, etc. are properly considered.

Synopsis of Midwifery and Gynecology. By ALECK W. BOURNE, B.A., M.B., B.CH. (CAMB.), F.R.C.S. (ENG.). Fourth edition. Pp. 434; 171 illustrations. New York: William Wood & Co., 1929. Price, $4.50.

*Practical Local Anesthesia.** By ROBERT EMMETT FARR, M.D., F.A.C.S. Second edition. Pp. 611; 268 illustrations. Philadelphia: Lea & Febiger, 1929. Price, $9.00.

Disorders of the Sexual Function. By MAX HUHNER, M.D. Third edition. Pp. 342. Philadelphia: F. A. Davis Company, 1929. Price, $3.00. Enlarged with a new chapter on Dysmenorrhea.

*Practical Massage and Corrective Exercises.** By HARTVIG NISSEN. Fifth edition, revised and enlarged. Pp. 271; 72 illustrations. Philadelphia: F. A. Davis Company, 1929. Price, $2.50.

*The Nervous Child.** By HECTOR CHARLES CAMERON, M.A., M.D. (CANTAB.), F.R.C.P. (LOND.). Fourth edition. Pp. 249; 8 illustrations. New York: Oxford University Press, American Branch, 1929.

*Pettibone's Physiological Chemistry.** By J. F. MCCLENDON, PH.D. Fourth edition. Pp. 368; 17 illustrations. St. Louis: The C. V. Mosby Company, 1929. Price, $3.75.

* Reviews of titles followed by an asterisk will appear in a later number.

PROGRESS

OF

MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

W. S. THAYER, M.D.,

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AND

JOHN H. MUSSER, M.D.,

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Clinical Classification of Congenital Cardiac Disease. — ABBOTT (*Lancet*, 1929, ii, 164) writes that clinicians do not always recognize the fact that congenital cardiac disease does not necessarily mean "blue baby" with its usual symptom complex. This particular type of congenital disease is of interest, but cannot be affected by the physician's skill since there are unalterable structural changes in the heart. There exists, on the other hand, a larger and much more important group of congenital cardiac patients to whom the word "acyanotic" applies. This group is of considerable importance to the physician because these patients have a relatively good expectation of life and may live to an advanced age without disturbances from their defect. It is for this reason that it is advisable to recognize this particular type. This "acyanotic" group is divided by her into two divisions. In the first there is mechanical interference with the circulation such as may be produced by pericardial defects, congenital heart block, pulmonary and tricuspid insufficiency, aortic and mitral stenosis, anomalies of the coronary arteries, and a few more rare conditions. In the second group the patients have arterial-venous shunt and possibly terminal or transient cyanosis with such defects as patent foramen ovale, multiple defects of the interauricular septum, localized defects at the base of the interventricular septum, patent ductus arteriosus, and localized defects of the aortic septum.

Antirabic Vaccination by Means of Desiccated Virus.—The director of the laboratories of Charity Hospital of Louisiana, D'AUNOY, reports (*Am. J. Pub. Health*, 1929, **19**, 986) upon the patients bitten by rabid animals treated during the past fourteen years with desiccated virus as prepared by the technique proposed by Harris and modified to a certain

extent. As a unit is designated the minimal infective dose; that is, the least amount of the desiccated material which within five days after preparation, kept at a temperature of −12° C., will cause paresis in a 2400 gm. rabbit within seven days following intracerebral injection. This minimal infective dose is between 0.002 and 0.004 mg. The initial dose is 250 units, doubling the quantity daily until a maximum of 2000 is reached. A total of 12 treatments is given the average patient, except in severe injuries of the face and scalp when 15 treatments, equivalent to 25,750 units, are given. There have been 5125 patients treated with the virus. About 25 per cent of the patients had a slight constitutional reaction and about 10 per cent, an allergic reaction. Three cases of treatment paresis occurred, one of which terminated fatally from an ascending infection of the urinary tract after paralysis of the lower extremities. There have been five deaths occurring in the series due to nonprotection. Of a total number of cases in which prophylactic antirabic vaccinations were given, 2380 of these were given to protect against injuries by proven rabid animals. The figures that have been compiled by D'Aunoy speak for themselves. They represent a really very remarkable series of patients protected against rabies.

SURGERY

UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

PHILADELPHIA, PA.

Treatment of Torticollis.—Howell (*British Med. J.* 1929, **2**, 714) says this paper has been written and these photographs of the cases before, during and after treatment have been shown in order to emphasize that torticollis may be prevented by careful antenatal examination of the mother to secure the simplest presentation avoiding natal injury. Further the younger the infant is, the sooner the cure. Lastly, the subcuteneous tenotomy of the sternomastoid muscle gives a complete, lasting scarless result.

Nodular Goiters—Their Relation to Neoplasia.—Graham (*Am. J. Surg.*, 1929, **7**, 163) believes that the development of the nodular goiter is in all probability dependent upon a single process or mechanism rather than upon multiple processes or mechanisms of fundamentally different character. Differences in degree of reversion growth, encapsulation and structural departure from otherwise normal thyroid tissue offer a satisfactory explanation of the gross and microscopic variations observed in nodular goiters. Such a conception obviates the necessity of invoking an embryologic defect for which insufficient objective evidence has been adduced to explain the so-called fetal adenoma of Wölfler. Nodular thyroids associated with endemic goiter, hypothyroidism and hyperthyroidism are intimately related in point of origin

to the hyperplastic phase of thyroid over growth rather than to the involutional phase. The latter may be a factor of some importance in determining the morphologic character of the end result. The process of nodulation may have its inception in fetal life, postnatal life, during puberty, adolescence or adult life. From a morphologic standpoint the end results of the process of nodulation, that is the encapsulated mass of nonlobulated thyroid tissue should be included in the category of benign glandular neoplasms.

Cases of Unsuspected Carcinoma of the Prostate.—BUGBEE (*J. Urol.* 1929, **22**, 363) noted that small carcinomata are found in the lateral and median lobes of the prostate which may be diagnosed only on microscopic section after removal. A more careful study of all prostates may make it possible to detect small suspicious areas leading to a prostatectomy in some cases where otherwise palliative measures might be continued. The sudden onset of retention in the presence of comparatively mild urinary symptoms may be suggestive of malignancy. Prostatectomy may be carried out quite as easily in these cases as in simple hypertrophy. Preliminary suprapubic drainage, allowing edema and infection to subside is an advantage. There is no evidence to point to the fact that the small amount of trauma incident to the removal of these prostates has caused a squeezing out of cancer cells into the lymphatics and a consequent spread of the disease.

Diagnosis of Perforated Peptic Ulcer.—VAUGHAN and SINGER (*Surg., Gynec. and Obst.*, 1929, **49**, 593) state that seventy-two patients diagnosed as having perforated ulcer were examined radiologically for pneumoperitoneum at the time of admission to the hospital. In 63 of the 72 patients the diagnosis of perforated ulcer was definitely established; 87.5 per cent of these had free intraperitoneal air as determined fluoroscopically. In the 9 remaining patients the evidence of perforated ulcer was not conclusive inasmuch as pneumoperitoneum was absent. Laparotomy was not performed and autopsy was precluded by recovery. The clinical picture in the nine unproven cases corresponds to that seen in perforations which become spontaneously sealed following the escape of a limited amount of gastric or duodenal content. The reason for the lesser frequency of pneumoperitoneum in these *formes frustes* cases is probably the same which explains the mildness of the course, *viz.;* a small leak with a trifling leakage.

Syphilis of the Stomach.—SINGER (*Am. J. Syph.*, 1929, **13**, 391) claim that a large number of cases presenting anatomically the features of linitis plastica have been reported as instances of gastric lues. Direct evidence pointing to a causal relationship between lues of the stomach and linitis plastica is obtained from the data in a case of syphilitic pangastritis reported by Windholz in which a patient was laparotomized, a biopsy obtained from the stomach, antiluetic treatment administered and the stomach secured some time later at autopsy. A comparison of the gross and microscopic features of the stomach at the time of operation with those found at autopsy indicated a transformation of a localized luetic gastritis into a circumscribed linitis plastica. In addition to direct testimony in direct evidence of a close association between

syphilitic inflammation and contraction of the stomach can be adduced from a clinical and anatomic and a combined clinicopathologic study. A joint clinicopathologic investigation has demonstrated that the more one seeks clinical indications of lues in the presence of an anatomic linitis plastica the more frequently does one find a positive Wassermann test and other indications of syphilis.

Chronic Cystic Mastitis.—Bloodgood (*Ann. Surg.*, 1929, **90**, 886) says that this is not a precancerous lesion any more than the lactating breast, but it may present microscopic pictures difficult to differentiate from cancer. More and more breasts are being sacrificed, the author believes, needlessly. In order to give all women who may have a cancerous lump in the breast at least 70 per cent chances of a cure we must bring them all under observation within a month. In probably 70 per cent of these cases any operation can be decided against by palpation alone. Of the 30 per cent in which the breast must be explored in one-half or more the benignancy of the lesion can be recognized by a combination of gross inspection and immediate frozen section.

THERAPEUTICS

UNDER THE CHARGE OF

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AND

SOMA WEISS, M.D.,

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The Therapeutic Effect of Insulin Administered by Mouth.—Following his experiences with the oral administration of adrenal cortex, Stephan (*München. med. Wchnschr.*, 1929, **38**, 1579) observed that when the dried substance of insulin or its salts were suspended in digestible fats and oils and administered in postabsorptive state, the blood-sugar level was lowered. Further observation showed that it was essential that bile should be present in the stomach if the insulin-oil suspension was to exert its effect. It was suspected, therefore, that an insulin-bile-acid combination is essential for the absorption of insulin after oral administration. Experiments substantiated this belief, and it was found that bile-acid combination of insulin is not destroyed by the stomach provided the latter is in postabsorptive state and the hydrochloric acid and ferments are neutralized. When such an insulin preparation is administered by mouth, it is absorbed as fast as from subcutaneous administration. The author claims that among the many combinations of insulin preparation with various derivatives of cholic acid, the most potent is the one which is prepared in a "special

manner" ("nach einem besonderen Verfahren") and is an addition product of insulin and of desoxycholic acid. The solution of this preparation is heat stable and can be boiled and sterilized. When it is administered subcutaneously it acts as does the usual commercial preparation. In order to neutralize the acid and fermented contents of the stomach, 2 grams of magnesium sulphate are administered twenty minutes previous to the administration of the insulin preparation. Following the oral administration of the insulin preparation to diabetic patients, the blood sugar falls, but slowly, and this fall may last as long as ten hours. If the administration of insulin is followed by the administration of food, the effect of the insulin becomes more prominent. The author therefore claims that orally administered insulin reaches its maximal effect if the "gastrointestinal reflex" is active. The effect of the preparation on diabetic patients is different from that on normal subjects. In severe cases of diabetes, the effect is apparently more pronounced than in mild cases. Apparently for each case there is an optimal dose for oral administration. Doses above this optimal amount exert no toxic effect. The therapeutic effect of this insulin preparation on the general condition of the patient is identical with that of the subcutaneous insulin therapy, according to the author's statement. The author does not claim that his observations solve the problem of the oral administration of insulin. The main purpose of the publication is to combat the pessimism hitherto persisting in the problem of the oral administration of insulin.

The Oral Administration of Insulin to Diabetic Children.—Ottow (*München. med. Wchnscher.*, 1929, **38**, 1584) reports her experiences with two diabetic children in using the preparation of insulin supplied by R. Stephan (see preceding abstract). She claims that the oral administration of insulin exerts a beneficial effect. The effect is slower than that after subcutaneous administration. The disappearance of sugar from the urine precedes the lowering of the blood-sugar level. Toxic effects are not noted.

The Treatment of Lung Abscesses by Direct Aspiration and the Injection of Neoarsphenamin.—Edel (*Med. Klin.*, 1929, **25**, 668) reports upon most strikingly favorable results in a series of 8 cases with lung abscesses which were treated by means of aspiration of the abscesses through a needle passed through the chest wall. Following the aspiration the syringe is detached and a solution of neoarsphenamin is injected directly into the cavity. The dose of neoarsphenamin begins with 0.15 gm. and progressively is raised to a maximal dose of 0.6 gm., an interval of four or five days elapsing between successive injections. The injection is followed promptly by a clearing up of the fetor, a general improvement in the patient's condition, a fall in the temperature and a very rapid evacuation and healing of the abscess cavity. A similar direct injection of neoarsphenamin gives equally satisfactory results in the treatment of infected bronchiectatic cavities. The injection into this cavity, however, is made through the trachea after cocainization. This method of treatment lies between the true surgical procedure which has such a very high mortality and the very unsatisfactory medical methods which demand so long a period of time and yield such poor results.

PEDIATRICS

UNDER THE CHARGE OF

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OF PHILADELPHIA.

Irradiated Foods and Irradiated Ergosterol. — BLUNT and COWAN (*J. Am. Med. Assn.*, 1929, **93**, 1301) discuss these subjects rather completely, and inasmuch as newer products often find unexpected favor, it is necessary to register warning with those products in which unfavorable results have been seen from overdosage. These authors state that the enthusiasm for irradiated ergosterol must be tempered with caution, since like many other potent drugs large doses may be distinctly dangerous. This danger is comparable to that found with the glands of internal secretion such as the thyroid and pancreas; small doses of which are absolutely essential to normal physiologic activity but which in large doses act as violent poisons. This comparison is more vivid if the theory is believed that the vitamin D promotes calcification through the stimulation of the parathyroid gland. It has been shown that exceedingly large doses of vitamin D caused a rapid loss of weight followed by death within a short time not only in white mice but also in larger experimental animals, such as guinea pigs, rabbits, cats and dogs. As the result of overdosage these animals presented the same picture of definite and severe disease, namely, loss of appetite, rapid loss of weight, severe emaciation and marked decrease of vigor. Diarrhea often developed and death usually followed in a comparatively short time. Studies of the tissues after death showed enormous deposits of calcium in the walls of the bloodvessels and the vital organs such as the heart, stomach and kidney. This has been taken to indicate that there was stimulation of calcification to the point where the mineral was deposited in any and all kinds of tissue that would receive it whether or not it was needed or useful there.

The Comparative Value in Infant Feeding of Condensed, Fresh, Canned Natural and Whole Powdered Cows' Milk.—PEREZ (*Philippine Islands Med. Assn. J.*, 1929, **9**, 265) informs us that the milk supply and its control in the Philippine Islands are still most primitive. The milk supply control is entirely overshadowed by the public health progress along other lines. He states that in many communities throughout the islands there are no dairy farms nor even milch cows. This results in a condition of extremely high cost, scarcity and even absence of a supply of satisfactory milk. There is the further difficulty of handling and preserving milk in the home because of the absence of refrigeration. Because of these conditions the pediatricians of the Philippine Islands are forced to employ canned-milk preparations for infant feeding, and the various brands of different forms of canned-milk products manufactured in United States and Europe are widely used and are freely sold in even the smallest shops in the smallest

villages. The author studied the safety and usefulness in a number of these preparations in infant feeding. Of the various products used by him, powdered whole cows' milk seemed to be most satisfactory. The results were very encouraging, especially when it is remembered that the preparation of the formulæ has been carried out by extremely ignorant people. Because of his results the author feels that powdered whole cows' milk is a solution for the problem of artificially feeding infants under conditions such as exist in the Philippine Islands. As it is in powdered form, it can be transported anywhere without refrigeration.

The Therapeutic Value of Irradiated Milk in the Treatment of Rickets.—Watson and Finlay (*Lancet*, 1929, ii, 704) confirm the claims of numerous German writers concerning the value of irradiated milk in the prevention and cure of rickets. They were of the opinion that irradiated milk should not be used as a complete substitute for good fresh untreated milk. They found in rickets in children between the ages of two and five years that excellent results followed when the milk was used in strength varying from 1 part irradiated to 2 parts non-irradiated up to equal parts of the two products. They feel that the cure of the disease is established more quickly and effectively as well as economically by the use of irradiated milk than by the use of various irradiated commercial preparations. They suggest that there are indications that irradiated milk may prove of great value in other disorders than rickets, especially those incident to pregnancy and lactation, the menopause, malnutrition, injuries and surgical diseases of bone and certain forms of tuberculosis.

The Determination of the Value of Serum in the Treatment for Meningococcus Meningitis.—Wright, De Santis and Sheplar (*Am. J. Dis. Child.*, 1929, **38**, 730) found that the agglutination test did not give uniform results and was unreliable as a guide for determining the value of the certain serum against a specific strain of meningococcus. As other methods, such as the opsonic index and the complement-fixation test, have not been of proved value in this determination, therapeutic tests seems to be the only reliable method of determining the curative value of the serum against a specific organism. This test may result in fatality in the treatment of a series of cases. When a patient with a meningococcus meningitis fails to respond to treatment there is no justification for the conclusion that the strain of organism met is resistant to serum therapy; but the only justification is the conclusion that the serum used was not specific for that organism, and it becomes necessary to seek an effective serum. There appeared to be a loss of specificity against a certain strain of meningococcus when too large a number of strains have been used in the production of a polyvalent serum. A single intraspinous injection of 20 cc. of an effective antimeningococcus serum in each twenty-four hours proved adequate. Potency of the serum rather than frequency of injections seemed the essential factor for successful treatment. It is emphasized that the quantity of serum administered should usually be less by at least 3 or 4 cc. than the quantity of spinal fluid withdrawn. They also advised the administration of antimeningococcus serum in the cisterna magna when there is evidence of blockage in the spinal canal.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Nonspecific and Malarial Therapy in Neurosyphilis.—REESE (*Am. J. Syph.*, 1929, **13**, 348) reviews the therapy of paresis, mentioning particularly the use of tuberculin, vaccine therapy and the use of nonspecific agents, that is, peptone, milk turpentine, aolan, and sodium nucleinate. Including the more recent reports in the therapeutic use of intermittent fever and rat-bite fever, the author believes that the best results are obtained with malarial therapy, particularly when supplemented by tryparsamide, mercury and iodids. Reese uses 6 to 10 cc. of infectious blood by intravenous inoculation for the average patient. Reinoculations after eight to fifteen months are most successful when the infectious blood is introduced intramuscularly as well as intravenously. Determination of blood groups in donor and recipient is advisable. After the patient has had from three to six chills, the author routinely uses such cardiac stimulants as camphorated oil or caffeine. Digitalis is avoided because of the bradycardia it may induce in conjunction with the later quinine. Modifying the severity of the general reaction, small doses of quinine are given. This procedure, it is hoped, will have a tendency to lessen the mortality rate. Indications for interruption of the malarial infection are poor physical condition, intercurrent disease, jaundice, nasal or oral hemorrhages and an increase of the blood urea (O'Leary's urea-nitrogen index). Organic metabolic diseases, circulatory diseases with high-systolic and low-diastolic pressure and chronic alcoholism are contraindications to malarial therapy. Aortitis or myocarditis without decompensation is not always a contraindication. Reese comments on the complexities of the factors operating in malaria therapy. A disturbance of the vegetative reflexes results in the emigration of the leukocytes toward the seat of an inflammation, and the author visualizes a similar activity in and about the inflammation of the nervous system. If the effect obtained in paresis is due to increased omnicellular activity, such a hyperactivity is the result of altered vasomotoric equilibrium accompanying or following the malarial chill and not the result of fever or some questionable antibodies. The chills, by altering the vegetative balance of the vasomotor system, with resulting dermographism, peripheral leukopenia and a drop in blood pressure, produce a renewed and intense activity in areas of chronic inflammation. The majority of the cases treated were paresis. The author points out that the pathology in tabes dorsalis is so different from that of paresis

that it would be difficult to see how malaria could possibly change tract degenerations and their clinical manifestations. Improvement was obtained in 42 per cent of the men and 46 per cent of the women. Fair results were obtained in 23.8 per cent and a mortality rate of 4.6 to 8.5 per cent was encountered. The author defines a successful result in the therapy of paretics as a restoration of mental capacity, the control of the emotional sphere and a good insight into ethics and law. The ability to resume a lucrative occupation is the best gauge of such results. The writer warns against the malarial remittent paretic, however, as one who often lacks quick and sound judgment and is apt to err suddenly, and as such is not fitted for positions of responsibility which might make these exactions.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Uterine Retrodisplacement.—In the treatment of uterine retrodisplacements the pendulum has been swinging widely. A decade or two ago practically every retroverted uterus was given the benefit, if such it may be called, of a suspension operation. Such operations were extremely popular and there were few gynecologists worthy of the name who did not have a pet modification of some operation if they were not clever enough to have an operation named after them. It was gradually determined that many of the patients who had been subjected to such surgery were not relieved of their symptoms so that the reactionary element in the profession declared that very few suspension operations were ever indicated. As is usually the case, the proper attitude toward this subject is probably a middle course, using great discretion in the selection of cases. In an experience of twenty-seven years as head of the Department of Obstetrics and Gynecology in the University of Michigan Hospital, PETERSON (*Ohio State Med. J.*, 1929, **25**, 541) has records of 31,000 cases of all kinds to draw upon for information. Concerning movable retroversion he states that those who deride any treatment of such uteri on the ground that no symptoms arise from them are quite as wrong as those who claim that all such cases are cured by operation. Of course many of the symptoms formerly thought to be due to retroversion are in reality due to muscle strain dependent upon faulty posture, mechanical spinal faults and disease of the joints. No longer is it permissible to study the pelvis alone and ascribe all aches and pains in the back, groins and legs to pelvic lesions. One must have a working knowl-

edge of symptoms which may be expected from certain skeletal and postural defects. There is nothing mysterious about the technique of such examinations. One does not have to be a specialist to make a differential diagnosis between backache caused by faulty posture, sacroiliac strain and pelvic disease. In his clinic every patient is studied not only gynecologically but for a possible explanation of her symptoms because of faulty posture and skeletal defects. He believes that the man who is willing to assume the responsibility of an operation for a retrodeviated uterus ought to be willing to devote enough time to the study of his patient to determine whether her symptoms are due to faulty uterine position, intrapelvic disease or to faulty posture with resulting ptosis and muscle strain, subluxation of the sacroiliac joints or actual disease of the spine or pelvic girdle. Without a working knowledge of how to determine the conditions which may give rise to certain symptoms he is incompetent to determine whether or not the patient should be operated upon for her uterine condition. He does not assume that the position of the uterus is of no consequence, but in itself it may or may not be producing symptoms. If the case is usitable for operation he has found the Gilliam operation to be the most satisfactory technique.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Facial Paralysis Associated with Acute Otitis Media.—The appearance of a facial paralysis in the course of an acute otitis media is very uncommon. Less than 1 per cent of all otitic suppurative processes present involvement of the facial nerve. Most facial paralyses are of peripheral origin—presumably due to such compressive factors as congestion, hemorrhage or mild inflammatory exudates within or without the nerve sheath. In reporting 3 personally observed cases, MORWITZ (*Ann. Otol., Rhinol. and Laryngol.*, 1928, **37**, 1263) concludes from his experience and from a study of the literature that the prognosis in this type of case is very good, although disappearance of the facial palsy may be extremely slow; that the treatment of the facial paralysis is essentially that of the ear condition *per se;* and that the paralysis as a complication is not necessarily an indication for operation. Inasmuch as the peripheral fibers of the facial nerve show a marked tendency to regenerate, complete disappearance of the paralysis usually occurs in from ten days to six weeks. In prolonged cases, physiotherapy (galvanism) should be instituted.

Experiences Concerning Mucosus Otitis.—In a series of bacteriologic cultures from 288 operative cases, VOGEL (*Ztschr. f. Hals-, Nasen- u. Ohrenh.*, 1929, **22**, 357) found hemolytic streptococci in over one-half of

the cases and Pneumococcus mucosus (also known as Pneumococcus III and Streptococcus mucosus) on 52 occasions (18.2 per cent). An analysis of the clinical data of 50 of the "mucosus" cases showed that 40 were adults, and 10 were children. Twenty-five of the adults exhibited a typical picture of mucosus otitis, pursuing a progressive course and presenting but few symptoms. The duration of the infection was much shorter in the young than in the adults. In some children postauricular swelling was the first outstanding manifestation. The tympanic membrane was not perforated in 5 instances. Intracranial complications were noted in over one-half of the 50 cases. Meningitis occurred eleven times. The mortality was 24 per cent, and was much higher than the 7 per cent resulting from a mixed flora, even when Pneumococcus mucosus was included. The author could not substantiate Steutz's claim that this organism has a predilection for the normally pneumatized mastoid cells. In the aged, the asthenic and in certain diabetics, a pathologic process similar to the one produced by "mucosus" can be caused by other bacteria—notably, Streptococci, Bacillus friedländer and Bacillus proteus.

Tuberculosis of the Middle Ear.—Asserting that aural tuberculosis has not been sufficiently recognized in the past, due to the belief that it is a rare disease and to the difficulties of diagnosis with the older laboratory methods, Cox and DWYER refer to a previous report (*J. Laryngol., Rhinol. and Otol.*, 1916, **31**, 288) wherein, of 32 children with chronic otorrhea, cultures revealed the presence of Bacillus tuberculosis in 5 (15.6 per cent). In the present communication (*Arch. Otolaryngol.*, 1929, **9**, 414) the authors add 10 additional cases of aural tuberculosis from the discharges of whom the Tubercle bacillus was isolated and cultivated by the use of sodium hydrate in conjunction with Miller's medium—the basis of which is an extract of the lymph glands and spleen of laboratory animals. In discussing the various features of otitic tuberculosis the authors mention that the prognosis is not necessarily unfavorable, although the tendency to osseous necrosis, facial paralysis, labyrinthitis and tuberculous meningitis should be remembered; that in children the infecting agent is often of the bovine type, coming from cows' milk; that further investigation is needed to prove the true value of heliotherapy; and that "appropriate local, general and climatic treatment combined in suitable cases with injections of tuberculin, offers the best hope of a cure."

Spectrographic Examination of Pellagrins' Sera.—SCOTT, TURNER and MAYERSON (*Proc. Soc. Exp. Biol. and Med.*, 1929, **27**, 27) write that exposure to direct sunlight produces or intensifies the erythematous eruptions on the parts of the body exposed to the sun. Why this occurs is not known, but it has been suggested that it may be due to hematoporphyrin in the blood. To determine this point; whether or not hematoporphyrin was present in the serum, the sera from 13 patients with active pellagra were examined with a Hilger quartz spectrograph. They recite in their article the technique of the examination. As a result of their study they are able to state definitely that there is no difference between the spectra of normal and pellagrous sera and that hematoporphyrin is not present in the circulating blood of the pellagrous individual.

RADIOLOGY

UNDER THE CHARGE OF

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The Significance of Small Intestinal Stasis.—KORNBLUM (*Radiology*, 1929, **13**, 17) has been able to distinguish between two main groups of cases showing small intestinal stasis. The first is that group which has received considerable attention from roentgenologists and which manifests what is commonly spoken of as "ileal stasis." The characteristics of this group consist primarily in a delay in the advance of the head of the opaque meal. At six hours this usually has extended only as far as the cecum, and occasionally the entire meal is in the terminal ileum, the loops of which are not distinguishable except by palpation, and are then often found to be of larger caliber than normally. Some of the more common causes are colonic stasis, adhesions, neoplasms of the large bowel, and external pressure from abdominal and pelvic tumors. Probably the most important single factor causing ileal stasis is adhesions resulting from inflammatory conditions of the appendix. The second group of cases showing small intestinal stasis differs markedly from the first. The advancement of the head of the opaque column is variable. The most striking feature is the variety of forms assumed by the intestinal shadow. The opaque material, while seen occasionally as one continuous shadow, is more frequently broken up into segregated loops, the masses varying in size, shape and caliber. Quite as significant is the finding of gas distended loops. Causes of stasis in this group comprise adhesions, subacute and chronic peritonitis from cholecystitis or perforated ulcer, ascites, tuberculous peritonitis, primary lesions of the small bowel affecting its lumen, metastatic malignant lesions, morphin, and purely nervous causes including fear. Kornblum particularly emphasizes the frequency of stasis from malignant metastasis to the peritoneum, and the low-grade peritonitis of a nonmalignant nature which commonly occurs with ulcerative and infected cancers of the stomach and colon.

Evaluation of Heliotherapy in Tuberculosis.—WATSON (*Arch. Phys. Therap., X-ray, Radium*, 1929, **10**, 252) considers that heliotherapy is by no means indicated in all cases of tuberculosis. There are many tuberculous patients who should never use it. In general, direct sunlight is indicated in cases of extrapulmonary tuberculosis and contraindicated in cases of pulmonary tuberculosis. For no type of tuberculosis is heliotherapy a cure; but often, especially in the extrapulmonary cases, it is a very valuable, or even necessary, aid. Since it is not in itself a cure, heliotherapy should never be used to the exclusion of the

usual standard therapeutic measures. Never should it be forgotten that the direct rays of the sun are extremely powerful, and that, carelessly administered, they can effect great harm. Direct sunlight, in the same amount, affects patients differently—more differently, especially in the beginning of its use, than almost any other remedy. Obviously, therefore, it must be used, in every case, not according to any hard and fast rule, not according to any theoretically predetermined dosage, but according to the individual reaction. Heliotherapy is of the greatest value, and may be practised with the least chance of doing harm, in pure extrapulmonary tuberculosis, that is, in the so-called surgical tuberculosis without pulmonary lesion. It is of great value in extrapulmonary tuberculosis with coincident pulmonary lesion; but in giving it here one must be far more careful than in the uncomplicated surgical type, particularly as regards exposing the thorax. It is of great value in hilum gland tuberculosis, and in this type should invariably be used. It is of some value in some cases of the proliferative type of pure pulmonary tuberculosis; but here it must be employed with the greatest caution, lest it transform a favorable, stationary, or healing lesion into a rapidly progressing and fatal one. It is virtually never of value, and is often positively harmful, in the exudative type of pure pulmonary tuberculosis, as well as in all acute types; and in such cases, therefore, it ought never to be used.

Treatment of Hemorrhage from the Nonmalignant Uterus.—Norsworthy (*Am. J. Roent. and Rad. Therap.*, 1929, **21**, 336) emphasizes careful selection of cases. Adolescent hemorrhage at the beginning of the menstrual function with irregular daily bleeding, if mild, may be corrected by general attention, and ovarian, thyroid or pituitary extracts. Radium should not be used until these fail. In epimenorrhea (too frequent menstruation), menostaxis (the prolonged type), and menorrhagia from a small or normal-sized uterus may be treated with radium. Menorrhagia from an enlarged uterus, in the absence of infection, calls for curettement. Menorrhagia from an enlarged fibrous uterus, even in the young woman, when found to be the result of infection, will respond completely to no other treatment than removal of the uterus. It must not be forgotten that radium is a dangerous agent when used in or around the pelvis of young women. It should be used in girls or young women only in small doses, and not until simpler methods have failed. Routine irradiation in submucous fibroids is contraindicated; operative removal is the treatment of choice. In bleeding associated with adnexal disease, surgical operation is the safest treatment. In pernicious hemorrhage during gestation the spleen and thyroid gland should be irradiated. Contraindications to full doses of radium, in the absence of malignancy, are: (1) cachexia out of proportion to the loss of blood; (2) pelvic or peritoneal infection; (3) tumors rapidly increasing in size; (4) pedunculated and calcifying tumors; (5) submucous tumors which so distort the uterine cavity that easy introduction of the radium applicator is prevented; (6) age, while an important factor at either extreme, does not contraindicate its use; radium is a valuable agent in checking hemorrhage in young girls and elderly women do not react badly to it.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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A New Sign of Cerebellar Disease.—WERTHAM (*J. Nerv. and Ment. Dis.*, 1929, **69**, 486) finds that diadochokinesis, which is essentially an inability to perform rapidly alternating movements, can be distinguished from the ability to perform rhythmic movements correctly regardless of speed. This latter ability, he designates rhythmokinesis and has devised a test for its disturbance which enables one to make a graphic record of the changes. The disturbance of this ability, he designates as arrhythmokinesis. He tested a group of cases, including most of the varieties of conditions in which adiadochokinesis can occur, and found that arrhythmokinesis did not coincide with the occurrence of adiadochokinesis, although the speed of the performance of rhythmic movements in adiadochokinetic cases was often slower than normal. Since all of the cases showing arrhythmokinesis had definite involvement of the cerebellum, he believes that this function is more closely related to cerebellar disease than is diadochokinetic ability. He presents 5 cases in which the disturbance was present and in which the cerebellum was definitely involved, all confirmed by operation. He assumes that the mechanism is fundamentally the same as that underlying the adiadochokinesis of cerebellar disease and considers the disturbance to be primarily irregularly in amplitude of action currents, their continuation long after the mechanical movement has stopped, and considerable lack of synchronous relations between flexor and extensor action currents.

Contribution a l'Etude Anatomo-clinique de l'Amyotrophie Charcot-Marie.—MARINESCO (*Revue Neurologique*, 1928, **2**, 543) reviews the history of amyotrophy of the Charcot-Marie-tooth type and presents a case with pathologic studies following death. The patient was thirty years of age and had the first manifestations of his illness at the age of eighteen years. The progress of the disease had been irregular. At autopsy, the author found grossly the degeneration of the muscle group involved in the legs and arms. Histologically, there was a degeneration of the motor fibers in the peripheral nerves with changes in the anterior horn cells similar to those usually found after section of a nerve. They also found in the cord a degeneration of the tracts of Burdoch and Goll. This degeneration was scarcely apparent in the sacral region. It was increased slightly in the lower lumbar segments and in the upper segments practically obliterated the posterior tracts. In the thoracic region a similar condition held but in the lower cervical region the lesion

was less diffuse, affecting only those central fibers belonging to the tract of Goll. In the upper cervical region both Goll and Burdoch tracts were affected. In the spinal ganglia he found residual nodules and other changes suggesting a reaction similar to those found in posterior column, sclerosis generally. The muscles showed histologically changes which appeared to be of an autolytic character. On the basis of these findings the author considers that the lesion in the Charcot-Marie-tooth type of amyotrophy is primarily a lesion of the axones of the motor and sensory nerve cells showing itself by changes in the muscles and anterior horn cells secondary to the degeneration of the motor axones; and by the atrophy of the posterior columns and changes in the spinal ganglia which constitute direct manifestations of the sensory lesions.

An Investigation of a "Mind-reading" Horse.—RHINE and RHINE (*J. Abnormal and Social Psychology*, 1929, **23**, 449) present a study of Mrs. Fonda's horse, Lady, who was reputed to have telepathic powers. They present in detail a number of experiments that were carried on over a period of a year. In many of these experiments the controls were checked as carefully as is possible in such experimentation. The controls were aimed at ruling out any ability on the part of the agent to signal to the percipient either consciously or unconsciously, or for unconscious suggestions to be made by observers. They notice especially the sleepy, rather apathetic, appearance of the horse during the demonstrations and the ability of the horse to move directly to the required object, and so forth, in the tests. The passivity of the horse, they state, could be deepened so much as to render her apparently motionless and almost asleep. She could be awakened at any time by a sharp command or a touch of the whip and would become quickly a normal, active colt again. They conclude that their experiments are sufficiently well controlled to leave only an explanation of telepathic communication to account for the results.

On Myasthenia Gravis.—QUERIDO (*J. Nerv. and Ment. Dis.*, 1929, **69**, 522) presents a case of myasthenia gravis studied both clinically and pathologically. His case is quite typical, the characteristic pathologic findings in the muscles being present. However, he found that the cellular infiltration about the smaller bloodvessels contained leukocytes, lymphocytes, plasmatic cells, fibroblasts and ripe fibrous tissue with traces of hemorrhage, and that the walls of the vessels running through such foci were infiltrated with the same types of cells. He offers the hypothesis that myasthenia gravis is a general vascular disease defined pathologically as a perivasculitis chronica proliferans. Since the pathologic preparations in his cases correspond fairly closely with those described by other authors he feels that in former pathologic studies the authors have been misled by Weigert's original communication regarding the presence of lymphocytes. He has compared his preparations with microphotographs occurring in the literature, but since all of these were of low-power magnification it was impossible for him to determine the actual character of the cells in the foci. If the hypothesis is correct he believes that it will explain the great variety of manifestations which occur in this disease.

PATHOLOGY AND BACTERIOLOGY

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The Structural Changes of the Liver in Pernicious Anemia. A Contrast Between Relapse and Remission.—METTIER (*Arch. Path.*, 1929, **8**, 213) studied comparatively the histopathology of the liver in 20 patients with pernicious anemia not treated with liver substance who died during relapse with that in 5 patients treated with liver who died from intercurrent disease while the anemia was in partial or complete remission. The most marked difference was noted in the Kupffer cells, which were of normal size in remission but showed pronounced hypertrophy during relapse. Desquamation of Kupffer cells and phagocytosis of erythrocytes occurred in both stages but was not more marked than in other severe anemias or in infectious diseases. Siderosis which was marked in the liver cells and moderate in the Kupffer cells during relapse was greatly lessened during remission. Although megaloblasts occurred free in the sinusoids of the liver in the patients who died during a relapse, hepatic hematopoiesis was not found in any of the 25 organs.

Histologic Changes in the Spleen in Early Congenital Syphilis with Special Reference to the Origin of Anemia in this Disease.—WATSON (*Arch. Path.* 1929, **8**, 224) reports the histologic appearance of the spleen in 4 cases of congenital syphilis, 3 of which presented severe anemia during life. The endothelial cells lining the sinusoids as well as the macrophages free in their lumina contained both nucleated and mature red blood cells in addition to large amounts of hemosiderin. Normoblasts were of frequent occurrence, but there were no other signs of myeloid metaplasia. In 2 cases examined, the anemia was of a regenerative type while in one the presence of bilirubinemia was associated with an indirect van den Bergh reaction. The author believes that these observations, together with the histologic changes in the spleen constitute evidence that the anemias were hemolytic and imply that the spleen plays an important rôle in their origin.

The Identity of Human Leprosy and Rat Leprosy.—There has been a very great difficulty in advancing the study of leprosy, because of not having the benefit of animal experiments. The work of WALKER (*J. Prev. Med.*, 1929, **3**, 167) has shown that the microörganism of leprosy appears in many morphologic forms and that Hansen's lepra bacterium is a tissue stage of this organism which may appear as coccoid, streptococcoid, diphtheroid, rod and branching filaments in

cultures and that it belongs to the genus Actinomyces. The author believes that human leprosy is primarily a soil infection with this facultative parasite, probably through wounds in the skin. The occurrence of a similar disease in the rat stimulated WALKER and SWEENEY (*J. Prev. Med.*, 1929, **3**, 325) to study this disease, and they have been able to clarify many of the obscure facts relating to human leprosy. They emphasize the balanced relation existing between parasite and host, and their work helps to explain the spontaneous decline of leprosy under improved economic and hygenic conditions as well as anticipating the appearance of sporadic cases and a number of other previously confusing observations. A very important part of their evidence supporting the identity of these two diseases was the discovery of the high incidence of latent infections among rats, and suggests its probable existence in man.

HYGIENE AND PUBLIC HEALTH

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The Distribution of Endemic Typhus (Brill's Disease) in the United States.—MAXCY (*U. S. Pub. Health Rep.*, 1929, **43**, 3084) reviews briefly the history of typhus in North America and shows that cases have been reported from 16 states in the period 1915–1927. None of the cases was traceable to importation. The cases noted above do not include the many from the southeastern states. Georgia alone reported 127 cases in 1927. Generally speaking, the disease is now limited to the Atlantic seaboard and the Piedmont region adjacent. The report concludes with the following paragraph: The limitation of this disease geographically does not seem to be explained satisfactorily on the basis of direct person to person transfer or through the intermediation of the louse. Some agency other than man and his own parasites would appear to be responsible for the preservation of the virus. This agency, be it insect alone, or an insect which feeds upon some host other than man, must be correspondingly limited in its distribution, or at least its capacity for acting as a vector to man must be so limited.

Trachoma in the State's Health Program.—MOSSMAN (*U. S. Pub. Health Rep.*, 1928, **43**, 449) gives a brief historical review of trachoma work in the United States, pointing out that the first surveys were made in Kentucky and that these have been followed by curative and pro-

phylactic work, especially in West Virginia, Tennessee, Arkansas and Missouri, in all of which states the disease is particularly prevalent in certain sections, some communities being very heavily infected, while other communities are free, or relatively free. The situation in Missouri has been especially emphatically demanding attention because, since 1922, that state furnishes financial relief to blind persons to the extent of $300 per year per person; about 20 per cent pensioners are blind as a result of trachoma, and this feature of the blindness is costing the state about $200,000 per year in direct payments, without considering the economic loss in medical treatment and the loss of time of the individuals. In many communities the trachoma work is giving the people their first acquaintance with modern public health work of any sort. This leads either to the installation of full-time health department organizations, or to the amplification of the activities of organizations already in existence. The trachoma hospitals thus have four functions, as follows: (1) Clinical treatment of trachoma for the purpose of preventing damage to sight and of stopping the patient from being a spreader of the disease. Field surveys have shown that the results of treatment. (2) Study of the disease itself. We are constantly on the alert for improved methods of diagnosis and treatment. Although nothing revolutionary has been discovered, we believe that we have made substantial improvements both in accuracy of diagnosis and in effectiveness of treatment. (3) Education of patients in personal hygiene and disease prevention. Patients admitted to these hospitals receive careful treatment for trachoma and also instruction in personal hygiene, health, habits and general health education. They are enabled to go home relieved of their disease and trained to some extent at least to live in a clean, health-promoting manner. (4) Centers for field work. Trachoma surveys are made in the surrounding territory by the staffs of the hospitals, by means of examination of school children, and by community clinics. During recent months it has become the policy to have field clinics arranged by a Public Health nurse for the special care of trachoma cases who have been hospitalized or who, for some reason or other cannot, or do not need to, be given hospital treatment.

The Minimal "Chlorine Death Points" of Bacteria. I. Vegetative Forms.—Tonney, Greer and Danforth (*Am. J. Pub. Health*, 1928, 18, 1259) found that a large majority of the vegetatives types of organisms considered to be of sanitary importance in connection with water supplies, milk supplies, dish washing, bottle washing, and general disinfection, whether of intestinal or respiratory origin, are killed in a few seconds by rather small doses of free chlorin, when exposed in a suspension containing no organic matter or other substances that react with or absorb the chlorin. This was true for temperatures ranging from room temperature to within a few degrees of the freezing point of water. The amount of chlorin required to kill most of the intestinal pathogens studied under these conditions was 0.1 p.p.m., with the greatest destruction of the organisms occurring within the first fifteen seconds of exposure. The same amount of chlorine destroyed most of the pathogenic types of respiratory organisms tested. In each group, however, there were individual strains which were more resistant to

chlorine than the others, requiring more than 0.1 p.p.m. to accomplish their destruction. In the intestinal group of organisms, the most resistant type encountered was Bacillus coli. In the group of respiratory origin, three strains of hemolytic streptococci, out of 24 strains tested, required larger quantities of free chlorin for their complete destruction. All the resistant strains of streptococci were killed by 0.25 p.p.m. in fifteen to thirty seconds. It is probable that the apparently higher resistance of the streptococcic strains is due to the larger number of organisms used in order to secure consistent growths. From the standpoint of resistance to chlorin, Bacillus coli stands out among the organisms tested as the most suitable for use as an index of the effectiveness of chlorin disinfection. The requisites of such an index organism are: (1) that it be as resistant as, or somewhat more resistant to, free chlorin than the pathogenic organisms which are to be destroyed; (2) that it grow readily on simple media; (3) that it be readily recognizable by simple routine tests. From the standpoint of availability, rapidity of growth, and ready detection, Bacillus coli offers superior advantages as an index organism, and it is our feeling that is consistent absence in a menstruum after chlorine disinfection is valuable evidence of the destruction of the pathogens here studied. On the whole the experiments appear to furnish a satisfactory theoretical basis for the current practice of relying on the consistent destruction of Bacillus coli in water as a criterion of effective chlorination, and that they may also justify a more general application of the same criterion to the other type phases of chlorine disinfection now being developed, such as the washing of milk bottles and equipment and the washing of dishes and eating utensils.

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On the Oxidizing Power of Oils and Its Modifications Under the Influence of Oligodynamic and Radioactive Agents.—JAYME R. PEREIRA (from the Department of Pharmacology of the S. Paulo Medical Faculty, S. Paulo, Brazil). The oxidizing power of various vegetable, animal and mineral oils was determined by the following technique: 5 cc. of the oil were transferred to an Erlenmeyer flask, to which were also added 2 cc. of a 20 per cent solution of acetic acid and 28 cc. of a 10 per cent solution of potassium iodid. This mixture was violently shaken for a few minutes and allowed to stand in a dark closet for twenty-four hours, at the end of which time the free iodin was determined, using a $\frac{N}{100}$ solution of sodium thiosulphate in presence of starch. The results were expressed in terms of cubic centimeters of the thiosulphate solution used.

It was found that mineral oils are devoid of any natural oxidizing power. In regard to the vegetable and mineral oils, they presented enormous variations, not only among the different species, but also among the specimens of the same species. This may be due to the different methods employed in their preparation and, in all probability, to their adulteration for commercial purposes.

One specimen of almond oil (Escoffier Fils—Grasse, France) showed a very high oxidizing power (2.3 cc. of thiosulphate solution), while a specimen of castor oil (Carlo Erba—Milan, Italy) did not show any power at all.

Under the action of silver (porcelain rings covered on the outside and inside with a coat of metallic silver) both the almond oil and the cotton-seed oil showed alternate phases of reduction and oxidation, that is their oxidizing power was periodically decreased and increased during the exposure to the action of silver. Practically the same results were obtained with paraffin oil and distilled water, which have no natural oxidizing power. In this case both these two substances acquired oxidizing power which showed then the same fluctuations spoken of before.

Under the action of "radia" (an emanogenic substance used to radio-activate drinking water) similar results were observed.

The relationship between the oxidizing power and the antirachitic potency of certain oils which has been previously shown by several investigators in connection with ultraviolet irradiation, suggests that experiments must be done in order to determine whether the oligodynamic and radioactive agents are also able to increase the antirachitic potency of the oils or not. This will be done in future experiments.

Relation of Monocytes of the Blood to the Tissue Macrophages.—Eliot R. Clark and Eleanor Linton Clark (from the Laboratory of Anatomy, University of Pennsylvania). A portion of the life history and many of the morphologic characteristics and reactive powers of the tissue macrophages have been studied by observation, with highest microscopic magnifications, of living cells in the transparent tails of Amphibian larvæ. Individual cells were followed by uninterrupted observations of four to thirty-six hours' duration.

The differentiation of early mononuclear wandering cells from a strand of primitive mesoderm located just ventral to the developing notochord was followed in Axolotl larvæ, at a stage before the first appearance of vascular endothelium or of blood cells in the tail. The change of such early wandering cells, following phagocytosis of various substances, into typical large pigmented macrophages was observed.

The tissue macrophages were found to be actively migratory and exceeding phagocytic and to undergo amazing transformations in shape and size. Macrophages were also found to be the most resistant cells present in the region studied. They were never seen to die even in cases of degeneration of or of injury to large surrounding areas, involving all other types of cells present.

The permanent transformation of macrophages into any other form of blood or tissue cell was never observed.

When small amounts of cream were injected into the extravascular tissue of the tail typical pigmented macrophages migrated toward the

injected globules and actively engulfed them. In addition, smaller, clear mononuclears moved directly toward the injected cream and joined the macrophages in the active phagocytosis of the globules. Cells filled with cream globules remained near the injection site for several days, during which time the ingested globules became smaller and the cells became more pigmented. After several days all of the cells of the group were similar in appearance, that is, they all resembled typical macrophages.

Larger injections of cream into the tissue stimulated the migration of leukocytes from the vessel. Monocytes then wandered toward the cream globules and joined the macrophages and clear mononuclears from the tissues in ingesting the cream. Polymorphonuclears and lymphocytes migrated also, but their reaction toward the cream was so slight as to be negligible.

In order to distinguish positively between cells which have migrated from the blood and cells from the tissue carmin granules were injected into the blood stream and their phagocytosis by monocytes was followed in the living. Circulating monocytes retained the carmin for two weeks or longer. Using tadpoles whose circulating monocytes were marked with carmin, cream was then injected into the outside tissue in amounts sufficient to stimulate emigration from the vessels.

In addition to migration toward the injected cream of (unmarked) macrophages and clear mononuclears from the tissues, carmin-containing monocytes were seen to migrate from the bloodvessels toward the cream and to take part in its phagocytosis. The carmin-marked cells were followed for two weeks and were found to display all the properties of appearance, movement and phagocytic powers characteristic of typical macrophages.

From these experiments it appears that the monocyte and the macrophage are two phases of the same cell, and that after the first differentiation of early tissue mononuclears, the supply of tissue macrophages is added to by the migration of monocytes from the blood stream.

Regarding the source of the monocytes in the blood, our observations supply no data. No proliferation of endothelium to form free cells was seen.

The Influence of Irradiated Ergosterol on Thyroparathyroidectomized Dogs.—J. H. JONES, M. RAPOPORT and H. HODES (from the Department of Physiologic Chemistry, School of Medicine, University of Pennsylvania). It has been demonstrated[1] that dogs given a preoperative treatment of cod-liver oil live for several weeks after the removal of the parathyroid glands, although the level of serum calcium be low. This is unusual, as dogs from which the parathyroids have been removed usually die within two to five days following the operation. Unpublished data show that irradiated ergosterol acts in a similar manner. Hess, Weinstock and Rivkin[2] and Greenwald and Gross[3] have reported negative results from the administration of large doses of ergosterol after the glands have been removed. Any postoperative treatment must of necessity act rapidly if it is to prevent the death of an animal which would otherwise die in a few days. On the other hand, if the length of life is increased by treatment before operation, the chances

for beneficial postoperative treatment are enhanced. With this in mind dogs were given treatments with ergosterol before operation. After the concentration of calcium fell to a low level following the removal of the glands ergosterol was again given in large amounts. Brief description of the experiments follows: Three dogs were given from 10 to 20 mg. of irradiated ergosterol daily for varying periods of time before the removal of the glands. The treatment was discontinued at the time of the operation. The concentration of serum calcium gradually fell until it reached 5.37, 6.01 and 7.34 mg. per 100 cc., respectively. At these points ergosterol was given in quantities of 50 mg. daily. The calcium rose to 20.1, 17.75 and 15.75 in two, fourteen and three days respectively.

Having received such striking results with these animals, it was thought advisable to try the postoperative effect of ergosterol on animals which received no treatment before operation. The parathyroids were removed from 4 dogs which received no preoperative treatment. The concentration of calcium fell within two days to 5.78, 5.45, 5.85 and 7.16 respectively. The first 3 developed tetany and were given milk in addition to 50 mg. of ergosterol daily. The first dog of this series vomited everything that was given and died on the ninth day after operation. The serum calcium on the seventh day was 5.78. The other 2 that were given milk retained it and in a few days began to eat the regular ration, at which time the milk was discontinued. The serum calcium of these two dogs increased to 17.6 in ten days and 47.27 in fourteen days respectively. Fifty milligrams of ergosterol were given daily to the remaining dog, starting with a calcium level of 7.16. No milk was given this animal. On the fourteenth day the calcium was 21.6.

Hemoglobin determinations showed no marked change in blood concentration. The inorganic phosphorus was also followed without any noteworthy results, except in the case of the dog with the extremely high calcium. When the calcium concentration was highest the phosphorus was 19.05 mg. per 100 cc. of serum. These experiments would indicate that ergosterol does not cause the increase in calcium of the blood by stimulating the parathyroid glands.

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Some In Vivo Uterine Responses in the Unanesthetized Rabbit.—S. R. M. Reynolds (from the Department of Physiology, University of Pennsylvania and the University of Chicago). Despite the many studies of uterine activity heretofore reported, none have been made *in vivo* in the unanesthetized chronic animal under conditions such that graphic records of the activity might be obtained. At the suggestion of Dr. M. H. Friedman, this was undertaken. A uterine fistula was made aseptically in a nonpregnant rabbit doe by transection of the vagina 1 to 1½ cm. below the uterovaginal junction. The intact orifices of the uteri were then passed through a stab incision to the exterior

in the lower left abdomen. Records of uterine activity can be obtained from time to time in such preparations. For recording, an air-water system, consisting of a water-distended balloon connected through an adjustable reservoir to a Brodie bellows, is employed. While the unanesthetized animal is secured in a supine position, the balloon is placed $3\frac{1}{2}$ to 5 cm. within the uterine cavity, and from this records are obtained. Studies on several animals, extending from April to August, inclusive, show that there are marked variations in the type of activity obtained from time to time in the same animal. Thus, the uterus may be relatively quiescent; then within the space of several weeks it may exhibit a large rhythmical type of activity, while in a few weeks more the uterus may be inactive. It is possible that this change may be associated with variations in the sex cycle, but this was not tested. When pituitrin is intravenously injected an initial tetanus immediately follows which lasts three to five minutes. A period of *inactivity*, lasting from three to ten minutes, follows this. On the other hand, when pitocin (oxytocin) is injected there is *no* period of inactivity following the initial tetanus. If one administers pituitrin or pitocin at a time when the uterus is not spontaneously active, the uterus is refractory to the drugs, and responds only feebly. This is not the case in the excised uterine strip. Even though the fistula response may be small, nevertheless, it is characteristic for the two drugs respectively, as described above. The extent to which these results on the nongravid uterus may apply to the gravid uterus has not been determined, hence their applicability to the clinical use of these drugs cannot yet be estimated.

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